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Preface

The first chapter in Volume 75 is a survey of aromatic *N*-haloazoles written by the late Professor M. S. Pevzner (St. Petersburg State Institute of Technology). The *N*-haloazoles are of special importance as halogenating agents and this chapter provides the first systematic treatment of their utility together with the fundamental chemistry of their preparation and reactivity.

The general Dimroth arrangement refers to the translocation of heteroatoms either within the rings of fused heterocyclic systems or between a ring heteroatom and a substituent. The present chapter presents the first modern general review of the Dimroth rearrangement and is authored by Professor E. S. H. El Ashry and Drs. Y. El Kilany, N. Rashed, and H. Assafir, all of Alexandria University, Egypt.

The chemistry of the pyridazines has been covered by the Ljubljana (Slovenia) group in articles appearing in *Advances in Heterocyclic Chemistry* at about 10-year intervals. The previous two reports appeared in Volumes 24 and 49 of our series in 1979 and 1990, respectively. Dr. Patrik Kolar and Professor Miha Tišler have now covered recent work on this interesting and important ring system.

The last chapter of the present volume is the second of a trilogy on the chemistry of the 1,2,4-triazolopyrimidines. The first in this series, which appeared in Volume 73 of *Advances*, surveyed the chemistry of the 1,2,4-triazolo[4,3-*a*]pyrimidines. The present chapter is concerned with the 1,2,4-triazolo[4,3-*c*]pyrimidines and is once again authored by Professor M. A. E. Shaban and Dr. A. E. A. Morgaan of Alexandria University. The third part is scheduled to appear in a subsequent volume.

Finally, Volume 75 is an "Index Volume." It therefore contains cumulative title and author indexes for the whole series, Volumes 1–75 of *Advances in Heterocyclic Chemistry*, together with the subject index for Volumes 71–75, ably compiled by Dr. Peter Kennewell. The last subject index was in Volume 70, which contained subject index entries for Volumes 61–70.

ALAN R. KATRITZKY

ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 75

Aromatic *N*-Haloazoles

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I. Introduction

The chemistry of aromatic *N*-haloazoles, as distinct from that of *N*-haloamines and *N*-haloamides (70CRV639; 90HOU586), has not been reviewed previously. Some aspects of the preparation of *N*-haloazoles were considered in recent reviews on the halogenation of heterocycles [93AHC(57)291; 94AHC(59)245]. Although in many ways similar to *N*-haloamines and -amides (*N*-halosuccinimides and -phthalimides), *N*-haloazoles have some characteristic chemical properties arising from the aromatic nature of the parent heterocycle.

In some cases *N*-haloazoles are intermediates in the electrophilic halogenations at carbon atoms of the heteroring.

This chapter deals with *N*-haloazoles in which the halogen atom is bound to the aromatic azole ring, excluding cyclic *N*-haloamines, *N*-haloamides, and some other analogous nonaromatic systems.

II. Methods of Synthesizing *N*-Haloazoles

A. The Mechanism of *N*-Halogenation of Azoles

A general method for preparing *N*-haloazoles is the halogenation of the corresponding azoles in a neutral or anionic form with halogens or their derivatives containing a formally positively charged halogen atom.

Detailed studies have not been carried out, but *N*-halogenation may be regarded as an electrophilic substitution. Moreover, a variety of complex reaction pathways in which *N*-haloazoles are intermediates for *C*-halo derivatives must also be considered. The intermediate *N*-haloazoles are often difficult to isolate or even detect. The first stage of the reaction between the halogen and azole is the formation of a donor–acceptor n–σ complex where the halogen is coordinated at the unshared electron pair of the "pyridine" nitrogen (in a neutral molecule) or the "pyrrole" atom (in the azole anion). The formation of donor–acceptor complexes of iodine with imidazole was established experimentally (76ZOB2576; 77ZOR2013; 81MI1; 84MI1), and their structure was considered by quantum-chemical methods (79ZOB1624). Further transformations of these complexes may proceed in several directions: (a) cleavage back to the starting substances; (b) rearrangement to a Wheland *C*-halogen intermediate (with subsequent deprotonation at the carbon atom leading to a *C*-haloazole); and/or (c) stabilization to an *N*-haloazole by loss of an *NH* proton.

The stability of *N*-haloazoles depends on the nature of the halogen, the heteroring, and on the substituents on the azole carbon atoms (see Sect. IVA).

B. *N*-Halopyrroles and Their Benzoderivatives

Usually halogenation of pyrroles and indoles yields *C*-halo derivatives, the products of oxydation, as well as polycyclic compounds [84CHEC(4) 213]. Reaction of a solution of pyrrole in CCl_4 with aqueous sodium hypochlorite yields *N*-chloropyrrole **1** stable for 2 weeks at 0°C (82JOC1008).

Analogously, pyrrole **2,** containing four electron-donating groups on the ring, with aqueous sodium hypochlorite and hypobromite give the corresponding *N*-chloro and *N*-bromo compounds **3a,b** (85CB4588, 85JHC1631). *N*-Fluoropyr-role **4** is prepared by treatment of the *N*-chloropyrrole **3a** with sodium fluoride in the presence of a catalytical amount of Sb_2O_3 (85CB4588) (Scheme 1). This reaction is unusual for *N*-haloazoles (see Section IV,B,3).

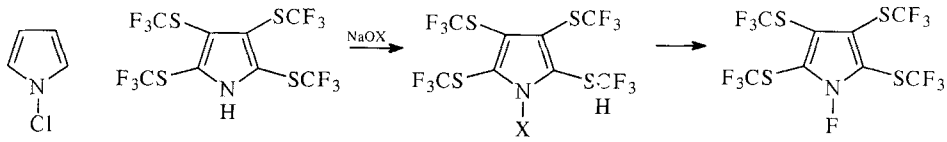
Indole and its derivatives in organic solvents (hydrocarbons, CH_2Cl_2, $CHCl_3$, and CCl_4) and aqueous sodium hypochlorite yield 1-chloroindoles **5,** 1,3-dichloroindoles **6,** and 3-H-3-chloroindole **7** [75JCS(CC)842; 78 JOC2639; 81JOC2054] (Fig 1).

N-Chloroindole **5** (R=H) is formed by chlorination of indole with dichloroxide (65NEP409386).

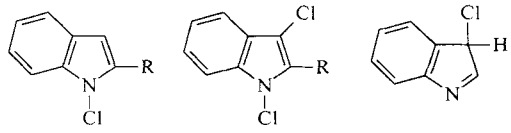
Chlorination of 5-substituted indoles **8** with sodium hypochlorite yields a mixture of 1-chloro- **9** and 1,3-dichloroindoles **10** [86H(24)1311]. Chlorination of compounds with electron-accepting substituents **8d–f** proceeds more smoothly and gives higher yields of *N*-chloroindoles **9d–f, 10d–f** than in the case of compounds with electron-donating substituents **8a–c** (Scheme 2).

The authors considered formation of compounds **9** and **10** to proceed by independent mechanisms. *N*-Chloro compounds **9** are formed by attack of hypochlorite anion on the neutral indole molecule (**8**) according to an S_E^i mechanism, proceeding through formation of the cyclic intermediate **11** (Scheme 3).

Electron-accepting substituents increase the acidity of the starting com-



Scheme 1



(5) (6) (7)

R=H, Me, Ph

FIG. 1

pound and, hence, favor the cleavage of the N–H bond in the intermediate. *C*-Chloroindoles **12** are formed as a result of the attack of the undissociated HOCl molecule on position 3 of the indole according to an S_E2 mechanism. These monochlorides then convert to 1,3-dichloroindoles **10** through an intermediate such as **11,** whose formation is favored by the presence of the electron-withdrawing chlorine atom in position 3 (Scheme 3).

N-Bromoindoles **14** were synthesized by bromination of 2-ethylsulfonyl-3-methyl- and -3-phenylindoles **13** with *N*-bromosuccinimide (77CPB2350) (Scheme 4).

Chlorination of carbazole with sodium hypochlorite in CH_2Cl_2, $CHCl_3$, or CCl_4 yields 9-chlorocarbazole **15** (87JOC173).

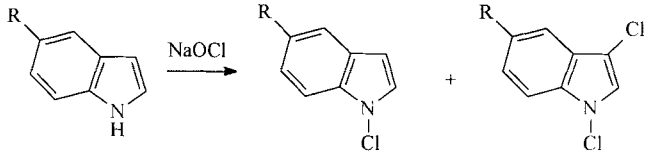
C. *N*-HALOPYRAZOLES

1. *N-Chloropyrazoles*

N-Chloropyrazoles **16** and **17** were obtained by chlorination of pyrazoles substituted with electron-accepting groups [56LA(598)186; 80JOC76] (Scheme 5).

2. *N-Bromopyrazoles*

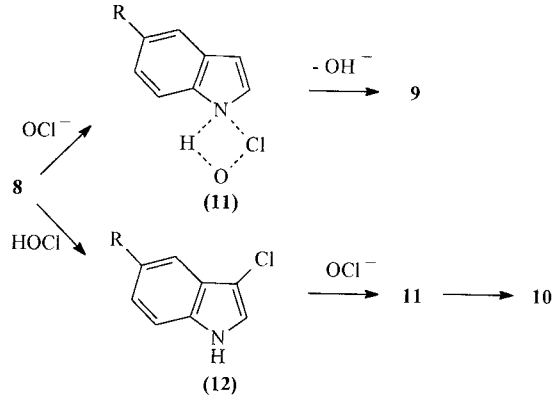
Bromination of pyrazole and methlpyrazoles yields unstable compounds having the *N*-bromopyrazolium bromide structure **18** [55LA(593)179] (Scheme 6).



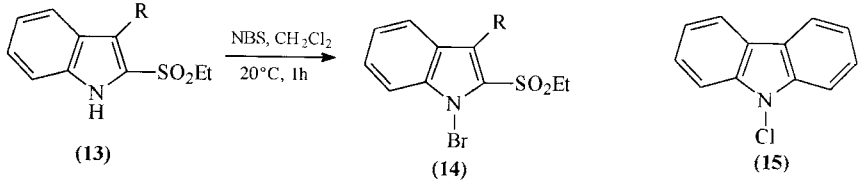
(8) (9) (10)

R = H (a); OMe (b); Me (c); Br (d); CN (e); NO_2 (f)

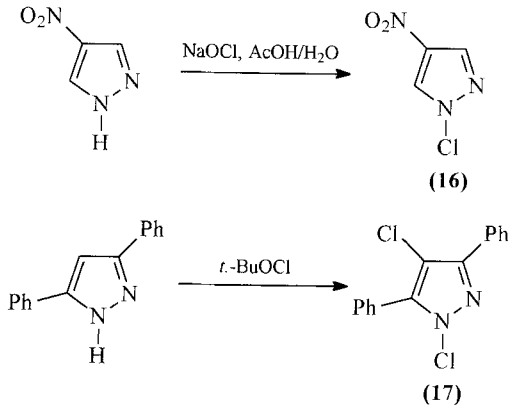
SCHEME 2



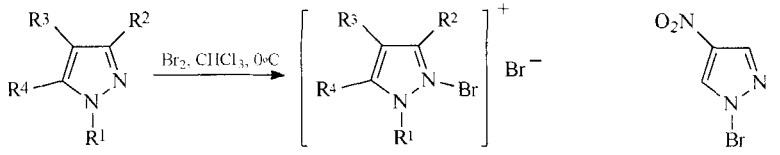
SCHEME 3



SCHEME 4



SCHEME 5



R1, R2, R3, R4 = H, Me

SCHEME 6

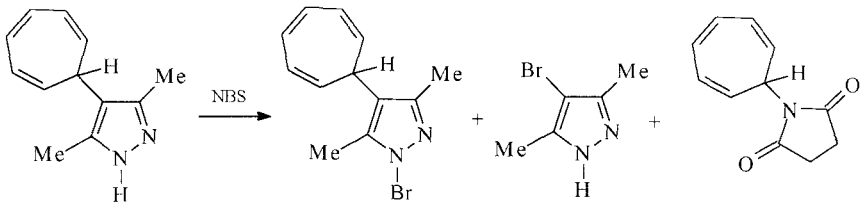
1-Bromo-4-nitropyrazole **19** is obtained by bromination of 4-nitropyrazole with sodium hypobromite in water–acetic acid [55LA(593)179]. 3,5-Dimethyl-4-tropylpyrazole is brominated with *N*-bromosuccinimide to form a mixture of *N*-bromoderivative **20,** 4-bromo-3,5-diethylpyrazole, and 7-tropylsuccinimide (64BCJ1018) (Scheme 7).

3. *N-Iodopyrazoles*

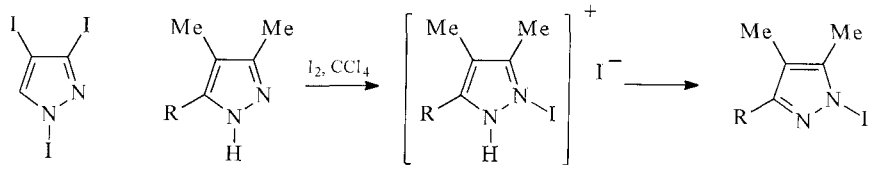
Unsubstituted pyrazole is iodinated by iodine in nitric acid in the presence of silver nitrate to form 1,3,4-triiodopyrazole **21** [55LA(593)200]. 3,4-Dimethyl- and 3,4,5-trimethylpyrazoles react with iodine with or without organic solvents to give *N*-iodopyrazolium iodides **22,** which with bases yield the corresponding free *N*-iodopyrazoles **23** [55LA(593)200] (Scheme 8).

Treating 4-iodopyrazoles with chlorine or bromine causes the substitution of iodine by the halogen through the formation of intermediate *N*-iodopyrazolium halides **24,** which under the action of bases are converted to *N*-iodopyrazoles **25** [56LA(598)186] (Scheme 9).

Synthesis of 1-iodo-3,4,5-trisubstituted pyrazoles **25** (R=Me, X=Cl, Br, I, Me) may be carried out by the reaction of the corresponding silver salts of pyrazole with iodine (70CB1949).



SCHEME 7



R=H, Me

SCHEME 8

D. *N*-HALOIMIDAZOLES AND -BENZIMIDAZOLES

1. *N-Haloimidazoles*

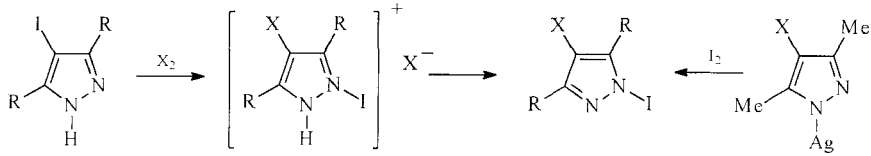
Imidazoles are easily halogenated at the ring carbon atoms to give mono-, di-, and trihaloderivatives [70AHC(12)103; 84CHEC(5)398; 93AHC(57)291], possibly though the formation of *N*-haloderivatives. *N*-Haloimidazoles were isolated and characterized in some cases. Thus, iodination of 2,4,5-trisubstituted imidazoles **26** yields considerably stable *N*-iododerivatives **27** (10CB2243) (Scheme 10).

Chlorination of 4-nitroimidazole in an alkaline medium gives unstable 1-chloro-4-nitroimidazole **28,** which decomposes in 1–2 days at 0°C (97ZOR 1847).

2. *N-Halobenzimidazoles*

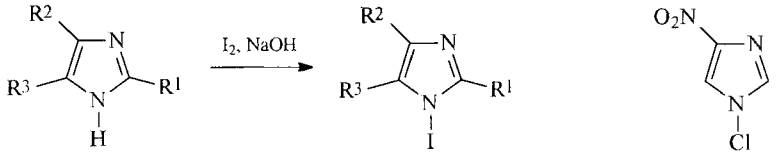
Chlorination of benzimidazole derivatives **29** having electron-accepting substituents in organic solvents or alkaline water yields the corresponding *N*-chlorobenzimidazoles **30** [70ZN(B)934, 70ZN(B)954] (Scheme 11).

Benzimidazole and 2-methylbenzimidazole are iodinated in alkali to form *N*-iodobenzimidazole **31** [63JCS2930; 81JCS(P1)403]. The same com-



R=H, Me; X=Cl, Br X=Cl, Br, I, Me

SCHEME 9



(26) (27) (28)

R1,R2,R3=Me (a); R1,R2,R3=I (b); R1=Me, R2,R3=I (c)

SCHEME 10

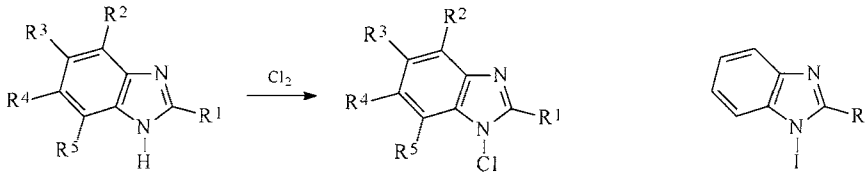
pound was obtained by treating 1-(tri-*n*-butylstannyl)benzimidazole with iodine chloride [83JOM(255)295] (Scheme 12).

E. *N*-HALO-1,2,3-TRIAZOLES AND -BENZOTRIAZOLES

1. *N-Halo-1,2,3-triazoles*

Chlorination of unsubstituted 1,2,3-triazole and 4,5-dimethyl-1,2,3-triazole with chlorine in organic solvents or treating the title compounds with an equimolar amount of sodium hypochlorite in acetic acid does not yield *N*-chlorotriazoles. Only hydrochlorides of the starting compounds and the products of ring cleavage were isolated [55LA(593)207]. 4-Methyl-1,2,3-triazole reacts with chlorine in chloroform to give only 4-methyl-5-chlorotriazole, but treating it with excess sodium hypochlorite and subsequent neutralization with sodium carbonate allows unstable *N*,5-dichloro-4-methyl-1,2,3-triazole **32a** (R^1=Me, R^2=Cl) to be isolated in 22% yield [55LA(593)207].

Under analogous conditions 4,5-dimethyl-1,2,3-triazole yields unstable *N*-chloro-4,5-dimethyltriazole **32b** (R^1, R^2=Me). *N*-Chloro-4,5-diphenyl-1,2,3-triazole **32c** (R^1, R^2=Ph), obtained by the chlorination of 4,5-

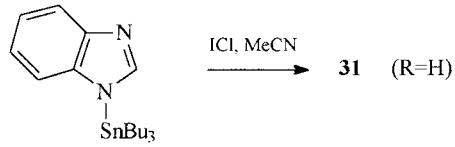


(29) (30) (31)

R1=CF3; R2, R3, R4, R5=H (a); R1=CF3, R2, R3, R4, R5=Cl (b); R1=CF3; R2, R3, R4=Cl, R5=H (c); R1, R2, R3, R4, R5=Cl (d)

R = H, Me

SCHEME 11



SCHEME 12

diphenyl-1,2,3-triazole with sodium hypoclorite in water–acetic acid, is more stable [79JCS(CC)419] (Fig. 2).

Unsubstituted 1,2,3-triazole reacts with excess sodium hypobromite to give *N*,4,5-tribromotriazole **33a** (R^1, R^2=Br), which is more stable than its *N*-chloro analog. Under the same conditions 4-methyl and 4,5-dimethyl-1,2,3-triazoles yield *N*-bromo derivatives **33b,c** [55LA(593)207].

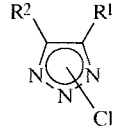
In contrast to chlorination and bromination, iodination of 1,2,3-triazoles yields stable *N*-iodotriazoles **34a–c**. Iodination may be carried out by treating the compound with iodine in an organic solvent, by sodium hypoiodite in an alkaline medium [55LA(593)207], or by iodine chloride in the presence of sodium ethoxide (70ZC220).

The position of the halogen in **32–34** was not established. Diphenyltriazole **32c** contains a peak (M-28)+ in its mass spectrum, which indicates a 1-chloroderivative, but the signals of the phenyl groups in an ^{1}H NMR spectrum of **32c** are equivalent, perhaps due to rapid N^1–N^3 exchange of halide or to its bonding at N^2 [79JCS(CC)419].

2. *N-Halobenzotriazoles*

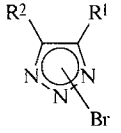
All four *N*-halobenzotriazoles are known. 1-Fluorobenzotriazole **35** was obtained by treating benzotriazole with excess cesium fluorosulfate (91T7447) (Scheme 13).

1-Chlorobenzotriazoles **36a,b, 37** were obtained by treating the corresponding benzotriazoles with sodium hypochlorite [68JCS(CC)1305; 69JCS(CC)1474; 78JCS(P1)909; 81IJC(B)898].



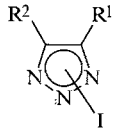
(32)

R^1=Cl; R^2=Me (a);
R^1, R^2=Me (b);
R^1, R^2=Ph (c)



(33)

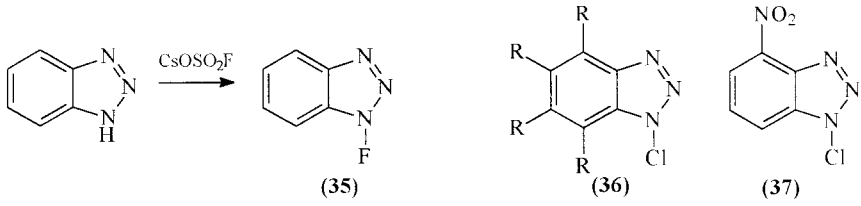
R^1, R^2=Br (a);
R^1, R^2=Me (b)
R^1=H, R^2=Me(c)



(34)

R^1, R^2=H (a);
R^1=Me, R^2=I (b);
R^1, R^2=Me (c)

FIG. 2



SCHEME 13

1-Bromobenzotriazole **38** and 1-iodobenzotriazole **39** were obtained by treating benzotriazole with sodium hypobromite and hypoiodite or, preferably, by halogen exchange from 1-chlorobenzotriazole and bromine or iodine [78JCS(P1)909] (Scheme 14).

Iodobenzotriazole **39** was obtained also by the reaction of 1-(tributylstannyl) benzotriazole with iodine chloride [83JOM(255)295].

F. *N*-HALO-1,2,4-TRIAZOLES

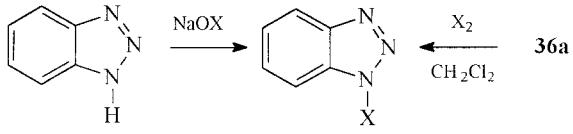
1. *N-Fluoro-1,2,4-triazoles*

1-Fluoro-3,5-dibromo-1,2,4-triazole is the only example of an *N*-fluoro-1,2,4-triazole. It was obtained by fluorination of 3,5-dibromo-1,2,4-triazole (68MIP1).

2. *N-Chloro-1,2,4-triazoles*

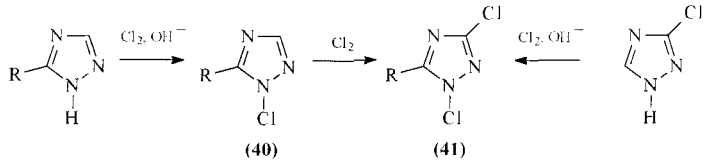
Unsubstituted 1,2,4-triazole and its derivatives with electron-donating substituents in the 3(5) position of the ring react with chlorine in alkali to give 1-chloro- and 1,3-dichlorotriazoles **40, 41** (67ZC184; 69ZC325). 1,3-Dichlorotriazole **41** was also obtained by chlorination of 3-chloro-1,2,4- triazole (69ZC325) (Scheme 15).

Chlorination of 1,2,4-triazoles may be carried out in organic solvents (diethyl ether, carbon tetrachloride) in the presence of acceptors of hydrogen



X=Br **(38)**; X=I **(39)**

SCHEME 14



(40) (41)

R=H (a), Me (b), Et (c)

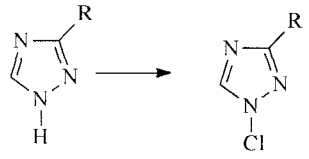
SCHEME 15

chloride (hydroxide, bicarbonate, or carbonate) (68MIP1; 69KGS1114; 72JPR923).

Other 3(5)-monosubstituted 1,2,4-triazoles are chlorinated at the N^1 or N^2 position depending on the nature of the substituents. In the presence of electron-donating substituents (R=Me, Et) a mixture of 1-chloro-3-R- **42** and 1-chloro- 5-R- **40** derivatives is obtained, the latter prevailing (80–85%) (72JPR923). Electron-accepting substituents in position 3 of the ring (R=Ph, Br, NO_2, Cl) cause the exclusive formation of 1-chloro-3-R-triazoles **42** (72JPR923; 9OIZV2814) (Scheme 16).

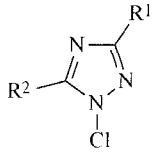
3,5-Disubstituted 1,2,4-triazoles with the same R^1 and R^2 substituents react with chlorine to form 1-chloroderivatives **43.** When R^1 and R^2 are different, the chlorine atom occupies the position close to an electron-donating substituent and far from an electron-accepting one (68MIP1; 69KGS1114; 72JPR923; 90IZV2814).

In addition to chlorine, the derivatives of sodium hypochlorite, hypochloric acid, and tertbutyl hypochlorite are used as chlorinating agents (68MIP1). In the reaction of chlorine in aqueous alkali with a triazole, hypochloric acid is the chlorinating agent. The alkali provides neutralization of hydrogen chloride and drives the equilibrium formation of HOCl resulting from the reaction of chlorine with water (72JPR923).



(42)

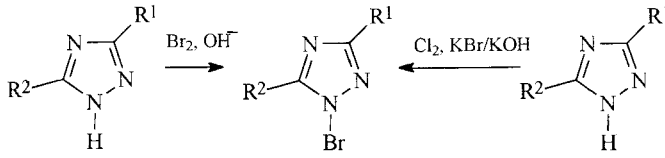
R=Ph (a), Br (b), NO_2 (c), Me (d), Et (e)



(43)

R^1, R^2=Cl (a); R^1, R^2=Br (b), R^1, R^2=CH_2Ph (c); R^1, R^2=Me (d); R^1, R^2=Et (e); R^1, R^2=Ph (f); R^1=Cl, R^2=Br (g); R^1=Ph, R^2=Me (h); R^1=Ph, R^2=Et (i); R^1=NO_2, R^2=Cl (j); R^1=NO_2, R^2=Br (k); R^1=NO_2, R^2=Me (l)

SCHEME 16



(44)

R^1=H, NO_2, Br, Cl, F, $C_6H_5CH_2C_6H_4CH_2$
R^2=H, Cl, Br, Me, COOMe

SCHEME 17

3. *N-Bromo-1,2,4-triazoles*

N-Bromo-1,2,4-triazoles **44** are prepared by treating a triazole with bromine in an alkaline medium (67CB2250; 68MIP1; 69KGS1114, 69ZC300, 69ZC325; 70JOC2635) (Scheme 17).

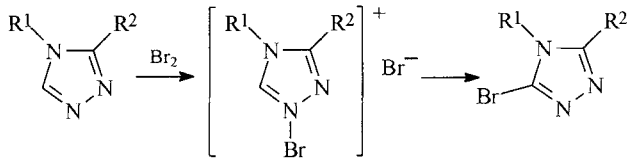
The position of the *N*-bromine is determined by the nature of the R^1 and R^2 substituents as with chlorination. Bromine enters the position close to an electron-donating and far from an electron-accepting substituent.

N-Bromotriazoles **44** may be obtained also by treating an aqueous alkaline solution of triazole and potassium bromide with chlorine [67BP1123947; 68FP1536979, 68GP(E) 60762].

On bromination of 4-substituted 1,2,4-triazoles, 1-bromo-4-substituted triazolium bromides **45** are formed as intermediates. Heating in water causes their rearrangement to 4-substituted 5-bromotriazoles **46** (75BSF647) (Scheme 18).

An analogous effect was observed for 1,3-disubstituted triazoles where the bromine atom is located at the N^4 heteroatom of intermediate **47** (75BSF647) (Scheme 19).

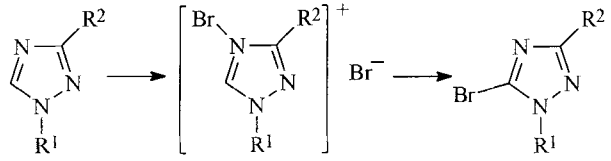
1,5-Disubstituted triazoles are brominated to give unstable intermediates, said to have structure **48.** Subsequent treatment leads to their decom-



(45) **(46)**

R^1=Me, Ph; R^2=H, Me

SCHEME 18



(47)

R^1, R^2=Me, Ph

SCHEME 19

position back to starting compounds and not to *C*-brominated products (75BSF647) (Scheme 20).

4. *N-Iodo-1,2,4-triazoles*

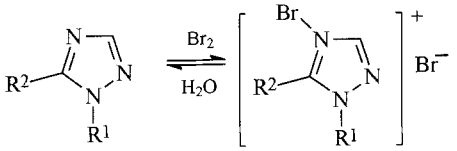
N-Iodo-1,2,4-triazoles cannot be obtained by treating the corresponding triazoles with iodine.

N-Iodocompounds **49** were synthesized by reacting 1,2,4-triazoles with iodine chloride or by treating an alkaline solution of triazole and potassium iodide with chlorine (68MIP1; 69KGS1114) (Scheme 21).

1-Iodo-3-nitro-5-methyl 1,2,4-triazole **50** was found among the products of the reaction of 1-chloro-3-nitro-5-methyl-1,2,4-triazole with isobutyl iodide (95ZOR113) (see Section IV, B,7).

G. *N*-HALOTETRAZOLES

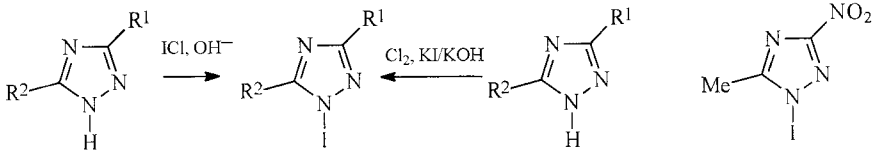
The reported attempts to obtain *N*-chloro-5-phenyltetrazole led to isolation of 1,4-dichloro-1,4-diphenyl-2,3-diazabutadiene **51,** probably through the formation of an intermediate *N*-chloro-5-phenyltetrazole with subsequent rearrangement to a *C*-chloroderivative and finally to the cleavage of the latter [79JCS(CC)419] (Fig. 3).



(48)

R^1, R^2=Me, Ph

SCHEME 20



(49)

R^1, R^2=Me, Ph

(50)

SCHEME 21

III. Structure and Spectra of *N*-Haloazoles

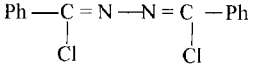
A. THEORETIC STUDIES

Theoretical studies of *N*-haloazoles by means of quantum chemistry (MNDO) were carried out for a series of *N*-halo-1,2,4-triazoles [98ZOR(ip)]. Charge distribution between the heterocycle and the halogen, bond length, bond order, and *N*–halogen bond energy depend mainly on the nature of the halogen (Table I). The most significant feature is the alteration in the sign and value of the charge on the halogen atom and the heterocycle on changing from *N*-fluorotriazole to other *N*-halotriazoles. This is connected with the changes in electronegativity of the halogens. The fluorine atom in *N*-fluoroderivatives has a small negative charge. That means that heteroring acts as an electron-donating group in relation to the halogen. In *N*-chloro-, *N*-bromo-, and *N*-iodotriazoles the halogen atom is positively charged, and the value of this charge increases on going from chlorine to iodine. From the calculations of the energies of *N*–halogen bonds it follows that the N–F bond in triazoles is much stronger than the N–Cl, N–Br, and N–J bonds, in agreement with the relative stability of *N*-halo-3-nitro-1,2,4-triazoles (see Section IV,A).

B. MOLECULAR SPECTRA

1. *Vibrational Spectra*

Infrared spectra of *N*-haloazoles usually are presented without detailed discussion. The main frequences are located in ranges characteristic of the



(51)

FIG. 3

TABLE I

ATOMIC CHARGES, BOND LENGTHS, ORDERS, AND ENERGIES OF THE N–HALOGEN BOND FOR SOME 1-X-1,2,4-TRIAZOLES [98ZOR(IP)]

		Atomic charges (e)						X-N bond parameters		
Compound	X	N-1	N-2	C-3	N-4	C-5	X	Bond length (Å)	Bond order	Bond energy (eV)
1-X-1,2,4-triazole	F	−0.07	−0.10	0.01	−0.24	0.13	−0.04	1.283	0.958	−15.98
	Cl	−0.17	−0.11	0.00	−0.24	0.11	0.11	1.690	0.915	−11.64
	Br	−0.23	−0.12	0.00	−0.24	0.11	0.18	1.780	0.892	−11.58
	I	−0.35	−0.13	0.01	−0.25	0.10	0.33	1.962	0.826	−11.73
	H	−0.20	−0.14	0.00	−0.25	0.08	0.24	1.003	0.889	−13.34
1-X-3-NO_2-1,2,4-triazole	F	−0.05	0.00	−0.02	−0.16	0.14	−0.02	1.283	0.963	−16.02
	Cl	−0.16	−0.01	−0.03	−0.17	0.12	0.14	1.690	0.913	−11.71
	Br	−0.22	−0.01	−0.03	−0.17	0.12	0.22	1.780	0.885	−11.60
	I	−0.34	−0.03	−0.03	−0.17	0.11	0.36	1.968	0.868	−11.56
	H	−0.18	−0.04	−0.04	−0.17	0.09	0.25	1.007	0.882	−13.23

particular classes of heterocycles and carbon-bound substituents. The main difference from the IR spectra of starting azoles is the disappearance of N–H bond vibrations (3500–3200 cm^{-1}) [69JCS(C)1474; 78JCS(P1)909; 85CB4588, 85JHC1631; 90IZV2814]. Infrared spectra of some *N*-haloazoles are listed in Table II.

2. *Electronic Spectra*

Ultraviolet spectra of *N*-haloazoles are presented without detailed theoretical consideration [69JCS(C)1474; 75JCS(CC)482; 78JOC2639; 86H(24)1311]. The absorption maxima of *N*-haloazoles are located in the ranges characteristic of the corresponding aromatic azoles. The differences in the UV spectra of *N*-chloroindole (λ_{max}265 nm), 3*H*-3-chloroindole (λ_{max}252 nm, shoulder), and 3-chloroindole (R = H) (λ_{max} 283 nm) are sufficient for kinetic studies of their transformation [75JCS(CC)482; 78JOC2639; 86H(24)1311].

TABLE II
IR SPECTRA OF SOME N-HALOAZOLES

Compound	ν_{max} (cm^{-1})	References
1-Fluoro-2,3,4,5-tetrakis-(trifluoromethylthio)-pyrrole	1573, 1501, 1163, 1094, 915, 783, 760	85CB4588
1-Chloro-2,3,4,5-tetrakis-(trifluoromethylthio)-pyrrole	1560, 1504, 1456, 1302, 1265, 1167, 1456, 1302, 1265, 1167, 1105, 1050, 756, 667, 475	85JHC1631
1-Bromo-2,3,4,5-tetrakis-(trifluoromethylthio)-pyrrole	1554, 1494, 1180, 1159, 1086, 755	85CB4588
1-Chlorobenzotriazole	1610, 1558, 1442, 1234, 1060, 1046, 774, 759, 745	78JCS(P1)909
1-Bromobenzotriazole	1610, 1589, 1269, 1213, 1158, 1001, 930, 788, 744, 653	78JCS(P1)909
1-Iodobenzotriazole	1610, 1588, 1444, 1268, 1189, 1166, 1000, 927, 785, 749, 648	78JCS(P1)909
1,4,5,6,7-Pentachloro-benzotriazole	1298, 1243, 1229, 1191, 1042, 1025, 984, 835, 814	78JCS(P1)909
1-Chloro-3-nitro-1,2,4-triazole	1560, 1530, 1490, 1440, 1430, 1320, 1230, 1190, 1120, 1030, 990, 880, 850	90IZV2814
1-Chloro-3-nitro-5-methyl-1,2,4-triazole	1565, 1485, 1320, 1150, 1100, 1060, 1010, 900, 860, 770, 720	90IZV2814
1,5-Dichloro-3-nitro-1,2,4-triazole	1580, 1480, 1440, 1420, 1320, 1120, 1030, 855, 710	90IZV2814
1-Chloro-3-nitro-5-brom-1,2,4-triazole	1550, 1480, 1410, 1300, 1150, 1080, 1060, 1010, 860, 770, 710	90IZV2814

3. *NMR Spectra*

Hydrogen-1 and ^{13}C NMR spectral data after 1967 were used to establish the structure of *N*-haloazole products. Hence, the character of ^{1}H NMR spectra of *N*-halobenzotriazoles (*35, 36, 38, 39*) confirms the location of the halogen at an N-1 heteroatom [69JCS(C)1474; 78JCS(P1)909; 91T7447]. Substitution of the proton at the heteroring nitrogen causes an insignificant downfield shift of a signal of the proton located at a neighboring carbon atom (72JPR923; 82JOC1008; 90IZV2814). A downfield shift of the ^{13}C signal was observed in ^{13}C NMR spectra of *N*-halopyrroles (82JOC 1008; 85CB4588, 85JHC1631) and *N*-chloro-1,2,4-triazoles (90IZV2814). Nitrogen-15 NMR spectral data are presented in only two examples for *N*-chloro-1,2,4-triazoles (90IZV2814). Substitution of the proton by chlorine at the N-1 heteroatom causes a negative shift of the signal. Fluorine-19 NMR spectra are published only for two compounds, 1-fluoro-2,3,4,5-tetrakis(trifluoromethylthio)pyrrole **4** (−35.39 ppm; 85CB4588) and 1-fluorobenzotriazole **35** (−18.41 ppm; 91T7447). The NMR spectra of some *N*-haloazoles are given in the Tables III–V.

4. *Mass Spectra*

Reported data on *N*-haloazoles are few (70OMS1532; 77CPB2350; 78JCS(P1)909; 85CB4588, 85JHC1631]. Mainly the peaks of molecular ions and of one or two fission ions are reported. In the spectra of 1-halopyrroles **3a,b** together with the molecular ion (M^+) the peak of the $(M–CF^3)^+$ ion was observed (85CB4588, 85JHC1631). 1-Bromo-2-ethylsulfonylindole **14** gives the molecular ion (M^+) (26%), the main peak of the fission ion [$(M-SO_2Et)^+$] (100%), and also intense peaks for [$M–Br+H)^+$] and [$M–SO_2Et-Br+H)^+$] (43%). The spectrum of 1-chlorobenzotriazole **36a** shows not only the molecular ion of the parent (M^+) (153/155), but also the molecular ion of benzotriazole (119) and its fragments (70OMS1523). The authors consider that the molecular ion of benzotriazole is formed not by the direct fragmentation of **36a** under the electron impact, but as a result of its reaction with the traces of water (Scheme 22).

The mass spectrum of *N*-chlorobenzotriazole, "purified" from the peaks of benzotriazole and the products of its fragmentation, contains the molecular ion (M^+) 153/155 (40%), the fission ions [$(M–N_2)^{+\bullet}$] 125/127 (20%), [$M–N_2$-Cl)$^{+\bullet}$] 90 (100%), and also the ions with m/e 63 (20%), 34, 33, 32, 31 (20%).

For other *N*-halobenzotriazoles and 1-chloro-4,5-diphenyl-1,2,3-triazoles **32c** it is characteristic that [$(M–N_2)^+$] ions are observed together with the molecular ion [78JCS(P1)909; 79JCS(CC)419].

TABLE III
NMR SPECTRA FOR SOME N-HALOPYRROLES

Compound	Chemical shifts, δ (ppm)			References
	^1H	^{13}C	^{19}F	
1-Chloropyrrole	6.08t 6.60t	124.0(C-2,5) 109.3(C-3,4)		82JOC1008
1-Fluoro-2,3,4,5-tetrakis-(trifluoromethylthio)-pyrrole		134.22(C-2,5)	−38.36(CF_3)	85CB4588
	—	124.40(C-3,4) 127.28(CF3) 127.12(CF3)	−39.80(CF_3) −35.99(N-F) −35.99(N-F)	
1-Chloro-2,3,4,5-tetrakis-(trifluoromethylthio)-pyrrole		131.4(C2,5)	−41.59(CF_3)	85JHC1631
	—	124.3(C-3,4) 128.1(CF3) 127.4(CF3)	−42.90(CF_3)	
1-Bromo-2,3,4,5-tetrakis-(trifluoromethylthio)-pyrrole		130.5(C-2,5)	−42.49(CF_3)	85CB4588
	—	123.8(C-3,4) 128.90(CF3) 127.83(CF3)	−43.41(CF_3)	
Pyrrole	6.22(t) 6.68(t)	118.2(C-2,5) 107.2(C-3,4)	—	84CHEC(4)1
2,3,4,5-tetrakis-(trifluoromethylthio)-pyrrole	—	126.2(C-2,5) 123.2(C-3,4)	−42.16(CF_3) −43.26(CF_3)	

IV. Chemical Properties

A. Stability

N-Haloazoles are thermodynamically unstable compounds. They must be handled with care because of possible spontaneous ignition and explosive decay [71CEN(49)30; 72JPR923; 78MI1].

Their stability is determined by the possibility to undergo transformations in several directions: (a) thermal decomposition with the destruction of the ring; (b) irreversible rearrangement to more stable *C*-haloazoles; and (c) dissociation of the *N*–halogen bond leading to starting materials. Reported data are insufficient to establish a complete scale of relative stabilities of *N*-haloazoles.

TABLE IV

^{1}HMR SPECTRA FOR 1-CHLORO-1,2,4-TRIAZOLES

Compound	Solvent	Chemical shifts, δ (ppm)	References
1-Chloro-1,2,4-triazole	C_6D_6	7.23(H-3); 7.76(H-5)	72JPR923
	CCl_4	7.78(H-3); 7.96(H-5)	72JPR923
1-Chloro-5-methyl--1,2,4-triazole	CCl_4	7.70(H-3); 2.50(5-CH_3)	72JPR923
1-Chloro-3-methyl-1,2,4-2triazole	CCl_4	7.95(H-5); 2.36(3-CH_3)	72JPR923
1-Chloro-5-ethyl--1,2,4triazole	CCl_4	7.78(H-5); 5-Et: 2.81(CH_2); 1.36(CH_3)	72JPR923
1-Chloro-3-ethyl--1,2,4triazole	CCl_4	8.00(H-5); 7.97, 7.33(Ph)	72JPR923
1-Chloro-3-phenyl-1,2,4-triazole	CCl_4	8.06(H-5); 3-Et: 2.70(CH_2); 1.29(CH_3)	72JPR923
1,3-Dichloro-1,2,4-triazole	$CO(CD_3)_2$	8.68(H-5)	90IZV2814
1-Chloro-3-nitro-2-1,2,4-triazole	$CO(CD_3)_2$	8.96(H-5)	90IZV2814

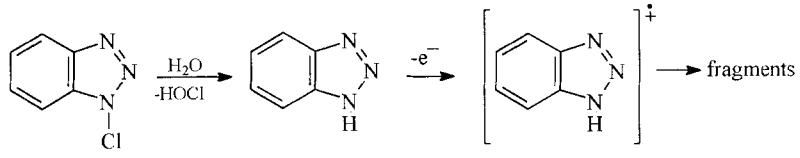
Thus, *N*-chloropyrrole and its benzoderivatives were obtained as solutions in inert organic solvents (alkanes, chloroalkanes); their stability at 0–20°C varies from several hours to several weeks [75JCS(CC)482; 78JOC2639; 81JOC2054; 82JOC1008; 84CHEC(4)213; 87JOC173]. The presence of electron-accepting substituents at the positions 3 and 5 of in-

TABLE V

^{13}C AND ^{15}N NMR SPECTRA FOR SOME *N*-CHLORO-1,2,4-TRIAZOLES (90IZV2814)

Compound	Chemical shifts, δ (ppm)[a]	
	^{13}C	^{15}N
1,3-Dichloro-1,2,4-triazole	152.02d(C-2)	−204.06d(N-1)
	149.10d(C-5)	87.23s(N-2)
		−121.75d(N-4)
1-Chloro-3-nitro-5-methyl-1,2,4-triazole	160.85s(C-3)	197.68q(N-1)
	159.25q(C-5)	−82.20s(N-2)
		133.22q(N-4)
1-Chloro-3-nitro-1,2,4-triazole	163.72d(C-3)	
	146.22d(C-5)	
1-Chloro-3-nitro-5-bromo-1,2,4-triazole	161.53s(C-3)	
	135.40s(C-5)	
1,5-Dichloro-3-nitro-1,2,4-triazole	160.26s(C-3)	
	146.90s(C-5)	

[a]Abbreviations: s = singlet; d = doublet; q = quartet.



(36a) m/e 119

SCHEME 22

dole ring increases the thermal stability of *N*-chloroindole solutions, but isolation of pure compounds is still impossible [86H(24)1311].

In contrast to *N*-chloroindoles, *N*-bromoindoles **14** with an electron-accepting substituent in position 2 (SO_2Et) are more stable and can be isolated (77CPB2350). Stability of *N*-halopyrroles and their benzoderivatives is connected with their ease of (a) oxidative destruction and (b) rearrangement to *C*-haloderivatives (see Section IV,B,2).

The series of *N*-chloro- and *N*-bromopyrazoles **16, 17,** and **19,** containing electron-accepting substituents (NO_2, Cl, I), are stable [55LA(593)179; 56LA(598)186; 80JOC76]. *N*-Iodopyrazoles **21** and **23** are more stable than their *N*-chloro- and *N*-bromo derivatives even in the presence of an electron-donating methyl group on the ring (70CB1949). The main factor relating to the stability of *N*-halopyrazoles is the ease of their transformation to *C*-halopyrazoles, although a role may also be played by their oxidative destruction [56LA(598)186].

In a series of *N*-haloimidazoles only 2,4,5-trisubstituted *N*-iodoimidazoles **27** are stable (10CB2243). *N*-Chloro-4-nitroimidazole is unstable and decomposes to nitroimidazole (97ZOR1847). Annulation increases the stability of *N*-haloimidazoles. *N*-Chlorobenzimidazoles **30** with electron-accepting substituents in the ring are rather stable [70ZN(B)934, 70ZN(B)954].

N-Iodobenzimidazoles **31** are stable even in the presence of the electron-donating methyl group in position 2 [63JCS2930; 81JCS(P1)403]. Their cleavage proceeds by breaking the *N*–halogen bond to form the starting benzimidazoles.

In the series of *N*-halo-1,2,3-triazoles, *N*-chloro compounds **28** are the least stable; more stable are *N*-bromo- **33** and *N*-iodo-1,2,4-triazoles **34** [55LA (593)207; 70ZC220].

The phenyl group in positions 4 and 5 of the ring increases the stability of *N*-chlorotriazole [79JCS(CC)419]. The cleavage of triazole **31c** is described in Section IV,B,2.

Annulation of 1,2,3-triazoles also increases the stability of their *N*-haloderivatives. All *N*-halobenzotriazoles are of considerable stability. *N*-Fluorobenzotriazole **35** is stable as a liquid at room temperature (91T7447).

N-chloro and *N*-bromo compounds **36a** and **38** have similar melting points (105–106°C and 114–116°C with decomposition, respectively), and *N*-iodobenzotriazole **39** melts at 214–216°C with decomposition [69JCS(C) 1474; 78JCS(P1)909].

For 1,2,4-triazoles, all the *N*-halo derivatives are relatively stable. Their stability is determined mainly by possibile rearrangement to *C*-halotriazoles and dissociation to the starting materials (67ZC184; 72JPR923; 90IZV2814).

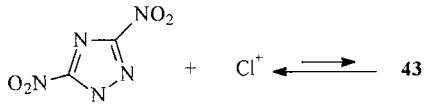
For 1-chlorotriazole **39** (R=H) the equilibrium involving its formation is shifted toward the final products (72JPR923). At the same time, 1-chloro-3,5-dinitro-1,2,4-triazole **43** cannot be prepared due to the high acidity of the starting dinitro compound (70KGS558) and the shift of the equilibrium is toward the starting compounds (90IZV2814) (Scheme 23).

In contrast to other azoles whose stability decreases from *N*-iodo to *N*-bromo and further to *N*-chloro derivatives, 1-chloro-3-nitro-1,2,4-triazoles are more stable that their 1-bromo and 1-iodo analogs. In this series the stability order is reversed (96UP1). Rearrangement of *N*-halo-1,2,4-triazoles is described in Section IV,B,2.

In summary, a series of stable *N*-haloazoles may be established. It includes *N*-chloro-, *N*-bromo-, and *N*-iodopyrazoles with electron-accepting substituents; 2,3,5-trisubstituted *N*-iodoimidazoles, *N*-iodobenzimidazoles, *N*-chlorobenzimidazoles with electron-acceptor substituents; *N*-iodo-1,2,3-triazoles; all *N*-halo-1,2,3-benzotriazoles; and *N*-halo-1,2,4-triazoles. Accumulation of electron-accepting substituents on the ring stabilizes *N*-haloazoles to a certain extent, but their stability decreases again because of the dissociation of these substances to the starting compounds. Annulation of an azole with a benzene ring also increases the stability of *N*-haloderivatives as does an increase in the number of heteroatoms in the ring from one to three. But further increase causes a marked decrease in stability as shown for tetrazoles.

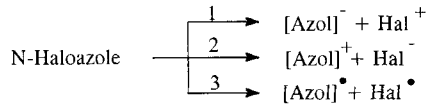
B. Chemical Transformations of *N*-Haloazoles

The reactivity of *N*-haloazoles is mainly determined by the feasibility of the cleavage of the *N*–halogen bond (Scheme 24).



43

Scheme 23



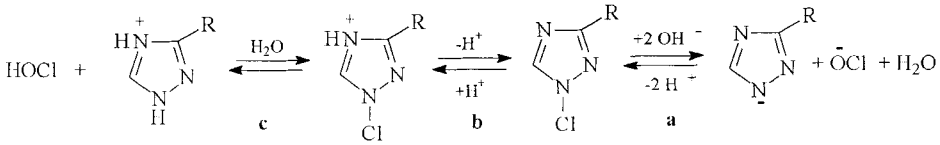
SCHEME 24

1. Reaction of *N*-haloazoles with compounds provoking the heterolysis of the bond to give a positively charged halogen ion and the azolate anion: this route takes place by the reaction of *N*-haloazoles with protic acids and inorganic reducing agents, by electrophilic halogenation and the addition to multiple bonds, and by the oxidation of organic substrates where the positively charged halogen is an oxidant in the first stage of the process (subsequent stages may proceed through radical formation).
2. Heterolysis of the *N*–halogen bond with the formation of halide anion: this process is favored by the electron-donating character of the heterocycle as is the case for pyrrole derivatives.
3. Homolytic cleavage of the *N*–halogen bond to form the azolyl and the halogen radicals. This pathway may take place in radical halogenation and the addition to a multiple bond, initiated by UV irradiation, or by means of radical initiators. This route may be found in some oxidative reactions (Scheme 24).

1. *Behavior of N-Haloazoles in Water and in Acidic and Basic Media*

The pathways of transformation of *N*-haloazoles in water and in acidic and basic media to a large extent depend on the basicity of azoles, the ease of heterolysis of the *N*–halogen bond, and the capability of further ring transformations.

Quantitative data on the basicity of *N*-haloazoles are absent, but it may be considered that it does not differ significantly from that of the starting heterocycles (90M11). From the quantum chemistry calculations of *N*-halo-1,2,4-triazoles and their NH analogs [98ZOR(ip)] it follows that the values of charges on the N^4 heteroatom (the protonation center) are similar (Table I). The possibility of protonation of *N*-haloazoles is confirmed also by their dissolution in acids, while in neutral medium they do not dissolve [1,2,4,5-tetraiodoimidazole (10CB2243); 1-iodobenzimidazoles (63JCS2930); 1-chloro-4-nitropyrazole [56LA(598)186]; 1-chlorobenzotriazole (90MI1); 1-chloro-3-nitro-1,2,4-triazole (96UPI)]. The solubility of some *N*-haloazoles in basic media is also reported [*N*-chlorobenzotriazole [69JCS(C)1474]; 1-chloro-3-nitro-1,2,4-triazole [96UPI]. After neutralization these compounds precipitate. The solubility in basic media may be caused by the dissociation of the *N*–halogen bond by nucleophilic attack of hydroxide ion on



SCHEME 25

the halogen atom. Transformations of the molecule of *N*–haloazole (for 1-chloro-1,2,4-triazole) are presented in Scheme 25.

The stages **a** and **c** may be irreversible due to the consumption of HOCl in subsequent reactions (thermal decomposition, halogenation, etc.). The final result of these processes may be the formation of the parent NH-azole (in protonated, neutral, or anionic form).

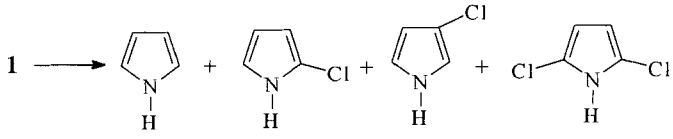
2. *Rearrangement of N-Haloazoles to C-Halo Derivatives*

Rearrangement of *N*-haloazoles to *C*-haloazoles is a typical reaction of *N*-haloazoles capable of halogenation at a ring-carbon atom. *N*-Chloropyrrole **1,** while heated with methanol, gives a mixture of pyrrole (30%), 2-chloropyrrole (~30%), 3-chloropyrrole (15–20%), and 2,5-dichloropyrrole (~10%) (82JOC1008). On the addition of the basic resin Amberlist A-21 to the reaction mixture the formation of 2-chloro-, 3-chloro-, and 2,5-dichloropyrrole sharply decreases (to 0.5–3%) (Scheme 26).

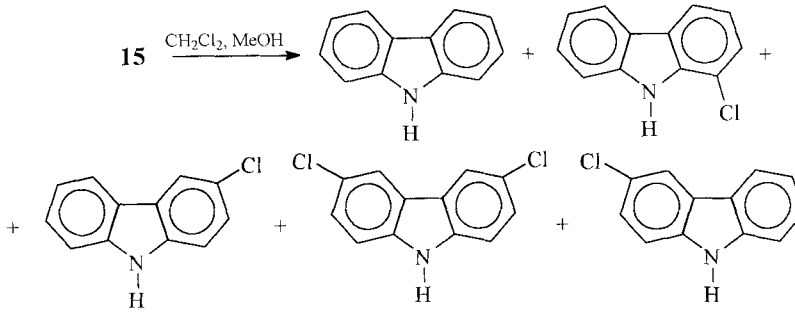
On the addition of pyrrole to the reaction mixture the yield of 3-chloropyrrole increases 10-fold.

The rearrangement of *N*-chloropyrroles to *C*-chloropyrroles may proceed by two pathways. The first one is the slow thermal rearrangement yielding 2-chloropyrrole, while the second one is the faster acid-catalyzed intermolecular reaction leading to 2- and 3-chloropyrroles in a 1.9-to-1 ratio. The acidity of the reaction mixture arises from the formation of HCl in the course of thermal decomposition of *N*-chloropyrrole (82JOC1008). An analogous scheme is proposed also for the formation of *C*-chlorocarbazoles from 9-chlorocarbazole **15** (87JOC173) (Scheme 27).

N-Chloroindoles **9** in alkaline ethanol are converted to 3-chloroindoles [78JOC2639; 81JOC2054; 86H(24)1311]. Kinetic studies showed that it pro-



SCHEME 26



SCHEME 27

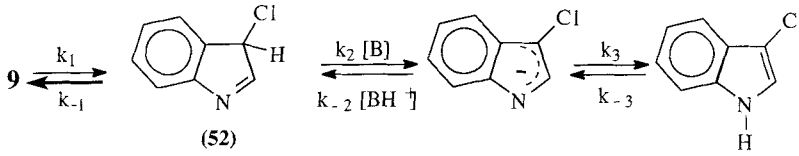
ceeds through the intermediate formation of 3-chloro-3*H*-indole **52** and is catalyzed by bases (Scheme 28). The rate-determining step is deprotonation of compound **52** (78JOC2639) (Scheme 28).

Rearrangement of 1,3-dichloroindole, **10** leads to 3,3-dichloro-3*H*-indoles **53** (81JOC2054). 3-Bromoindoles **54** are formed analogously from 3-R-3-bromo derivatives **14** (77CPB2350) (Scheme 29).

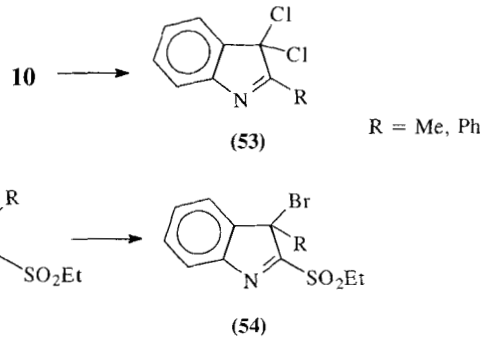
N-Halopyrazoles also easily form the products of rearrangement [55LA(593)200; 80JOC76]. 3,4-Dimethyl-5-iodopyrazole **55** is formed by heating *N*-iodo derivative **23** in the presence of 3,5-dimethylpyrazole, which plays the part of the halogen carrier [55LA(593)200]. 1,4-Dichloro-3,5-diphenylpyrazole **17** spontaneously undergoes a rearrangement to the more stable 4,4-dichloro-4*H*-pyrazole **56** at room temperature (80JOC76) (Scheme 30).

In the series of 1,2,3-triazoles fast rearrangement of *N*-bromo-4-methyl-1,2,3-triazole **33c** to 4-methyl-5-bromo-1,2,3-triazole **57** is described [55LA(593)207]. 1-Iodo-1,2,3-triazole **34a** yields 4,5-diiodo-1,2,3-triazole **58** on heating to 110°C in the presence of 3,5-dimethyl-1,2,4-triazole as a halogen carrier (70ZC220) (Scheme 31).

Heating 1-chloro-4,5-diphenyl-1,2,3-triazole **31c** in acetonitrile decomposes it to benzonitrile, 2,3-diphenyl-3-(4,5-diphenyl-1,2,3-triazol-1-yl) azirine, and phenylchlorodiazomethane [79JCS(CC)419]. This cleavage arises from the intermediate formation of the products of rearrangement of



SCHEME 28



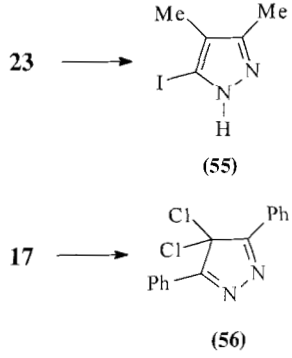
SCHEME 29

31c to a *C*-chloro derivative and its subsequent transformation in two directions: (a) cleavage of the ring and (b) evolution of nitrogen (Scheme 32).

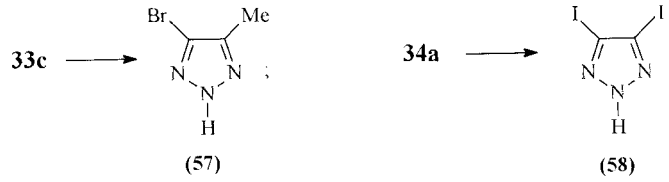
The transfer of halogen from nitrogen to a benzotriazole ring takes place in the reaction of *N*-chlorotriazole **36a** with 1-azabicyclo[2.2.2.]octane through the intermediate formation of a 1-chloroazonium derivative [76JCS(P1)741] (Scheme 33).

Rearrangement of *N*-halo-1,2,4-triazoles to *C*-haloderivatives is described in a series of reports. The possibility of formation of *C*-halo-1,2,4-triazoles depends on the reactions conditions; on the nature of the halogen; and on the presence, type, and location of substituents at the carbon atoms of the ring.

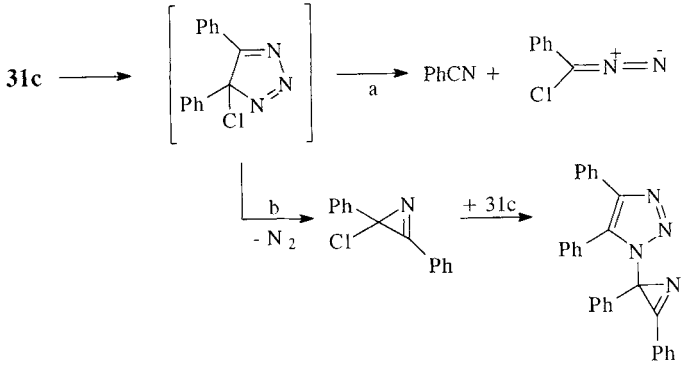
N-Chloro- and *N*-bromo-1,2,4-triazoles **42** and **44** are converted to *C*-halo derivatives by heating in inert solvents in the presence of benzoyl peroxide or by UV irradiation under conditions typical for a radical process (69KGS1114) (Scheme 34).



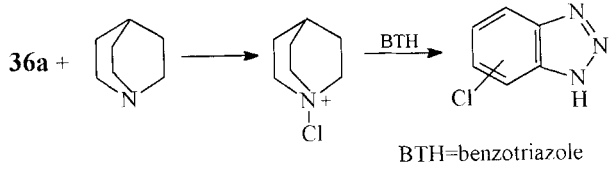
SCHEME 30



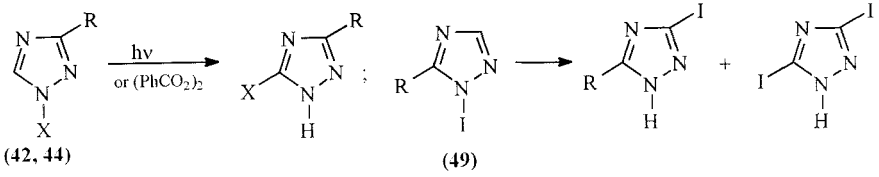
SCHEME 31



SCHEME 32



SCHEME 33



SCHEME 34

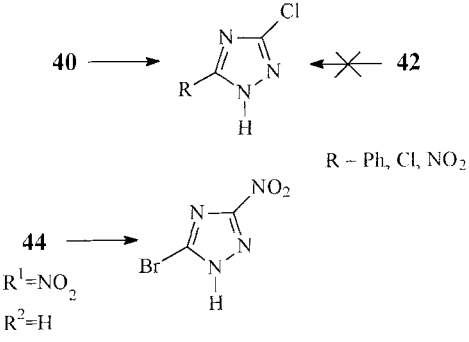
SCHEME 35

N-Iodo-1,2,4-triazole **49** in contrast to *N*-chloro and *N*-bromo derivatives does not react under these conditions (69KGS1114). Formation of 3-iodo- and 3,5-diiodo-1,2,4-triazole proceeds on heating to 150°C in the presence of 3,5-dimethyl-1,2,4-triazole as the halogen carrier (69ZC300; 70ZC220).

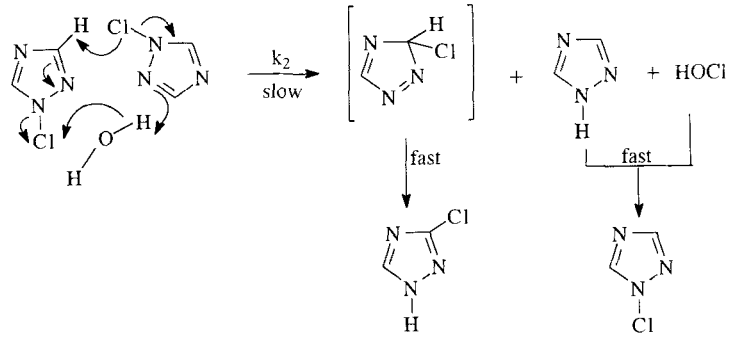
When the substituent in position 5 is absent, 1- and 4-substituted *N*-bromotriazolium bromides **45** and **47** are easily converted to 5-bromo-1,2,4-triazoles by heating in water (75BSF647) (Scheme 35).

Rearrangement of 1-chloro-1,2,4-triazoles to 3-(5)-chlorotriazoles takes place on heating in water or *tert*-butanol when electron-withdrawing substituents in the ring are absent. Such 1-chloro-5-R-1,2,4-triazoles **40** (R=H, Me, Et) yield 3-chloro-5-R-derivatives, but if R=Ph, Cl (72JPR923), or NO_2 (93ZOR2326) (compounds **42**), then only dehalogenation leading to NH-azoles takes place. However, *N*-bromo-3-nitro-1,2,4-triazole **44** gives the product of rearrangement on heating in basic medium (70JOC2635) (Scheme 36).

Kinetic studies of the rearrangement of *N*-chloro-1,2,4-triazole in water showed that this reaction is second order in *N*-chlorotriazole and is independent of pH in the range 2–7. The considerably negative value for the activation entropy (−20.6 cal/deg-mol) shows that a high degree of coordination of the rings is needed in the transition state. Therefore, the process may be an intermolecular transfer of halogen from the nitrogen of one ring to



SCHEME 36



SCHEME 37

the carbon atom of the other. Triazole and HOCl, formed in the process, quickly react to re-form *N*-chlorotriazole (72JPR923) (Scheme 37).

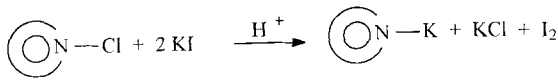
Hence, intermolecular rearrangement of *N*-haloazoles to *C*-haloazoles is an example of the halogenating properties of *N*-haloazoles (see Section IV,B,5).

3. *Reactions of N-Haloazoles with Reducing and Nucleophilic Reagents*

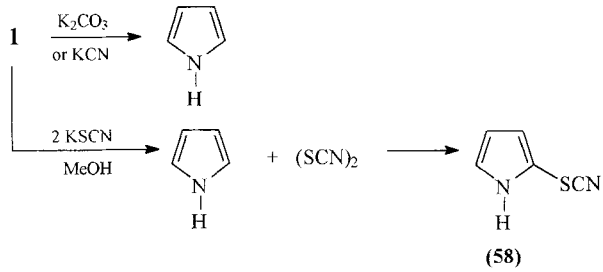
Reactions of *N*-haloazoles with reducing and nucleophilic agents often take place because these compounds formally contain a positively charged halogen leaving group. They easily react with typical inorganic reducing agents (iodide, bisulfite, sulfide, and hypophosphite ions and ammonia) to cleave the *N*–halogen bond; NH-azoles are formed [55LA(593)200, 55LA(593)207; 67CB2250, 67ZC184; 69KGS1114, 69ZS300; 70ZN(B)934; 77CPB2350; 90IZV2814]. Depending on the electron distribution in the azole molecule and the nature of the attacking nucleophile, reaction may involve other reactive centers of an *N*-haloazole.

Reactions of *N*-chloropyrrole, *N*-chloroindole, and *N*-chlorobenzotriazole with sodium or potassium iodide are used for their quantitative iodometric determination (78JOC2639; 82JOC1008; 90MI1) (Scheme 38).

N-Chloropyrrole **1** is easily dehalogenated by potassium carbonate and cyanide ion (82JOC1008). The introduction of a thiocyanate group in position 2 of the pyrrole ring is achieved with thiocyanate ion. The reaction pro-



SCHEME 38



SCHEME 39

ceeds through the intermediate formation of pyrrole and dithiocyanogen, which react to give 2-pyrrolyl thiocyanate **58** (82JOC1008) (Scheme 39).

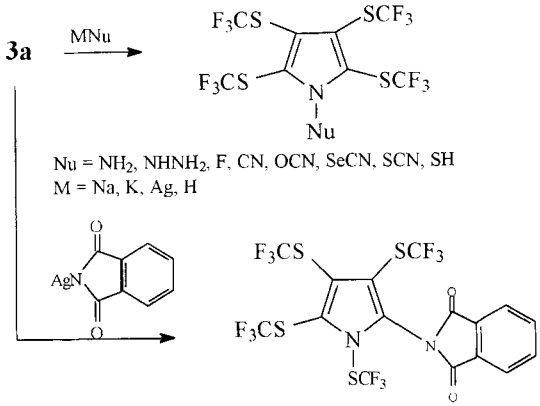
The presence of trifluoromethylthio groups on the pyrrole ring changes the direction of reaction of such an *N*-chloropyrrole with nucleophilic agents. 1-Chloro derivative **3a** reacts with nucleophiles to form the products of N-substitution (85CB4588; 89JFC265) (Scheme 40).

It is significant that tetrasubstituted *N*-chloropyrrole **3a** does not react as a chlorinating agent (85CB4588).

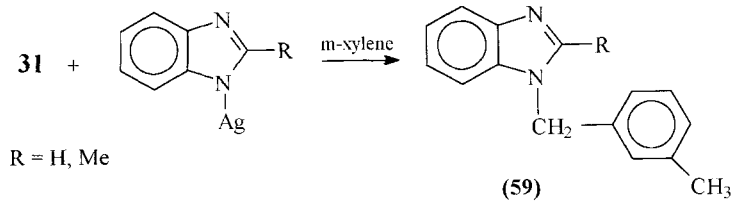
Reaction of *N*-chloropyrrole with silver phthalimide proceeds to introduce the phthalimide moiety in position 2 with the simultaneous migration of trifluoromethylthio group to nitrogen (85CB4588) (Scheme 40).

All the attempts to substitute the N-bound halogen by a nucleophilic moiety failed in other *N*-haloazoles.

Reaction of *N*-chlorobenzotriazole with alkali does not yield a 1-hydroxy derivative [69JCS(C)1474] (see Section III,B,1). Reaction of *N*-iodobenzimidazole or *N*-chlorobenzotriazole with silver or sodium salts of the cor-



SCHEME 40



SCHEME 41

responding azoles also does not lead to *N,N'*-bisazoles [69JCS(C)1474; 81JCS(P1)403].

Reaction of N-iodobenzimidazoles **31** with the silver salt of benzimidazole in boiling *m*-xylene yielded only the benzylated heterocycle **59** [81JCS(P1)403] (Scheme 41).

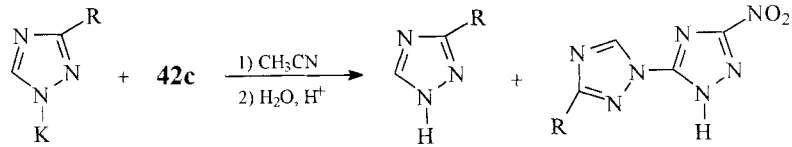
Reaction of 1-chloro-3-nitrotriazole **42c** with potassium salts of 3-bromo and 3-nitro-1,2,4-triazoles yields the NH-azole as the main product, with 5-10% of 1,5-bistriazoles, which are formed as a result of nucleophilic substitution of hydrogen in the position 5 of *N*-chlorotriazole (Scheme 42).

Reaction of 1-chloro-1,2,4-triazoles with chloride ion in acetonitrile results in complete dechlorination even at 1 : 100 [Cl^-]/[*N*-chloroazole] molar ratio. It is proposed that the reaction proceeds according to the scheme including a one-electron transfer from chloride ion to *N*-chloroazole to form *N*-chloroazolyl radical anion, and its fast decay to chloride ion and triazolyl radical, which removes a hydrogen atom from the solvent to give NH-azole. Chloride ion reacts with a new molecule of starting *N*-chloroazole to continue the reaction chain (90IZV2814) (Scheme 43).

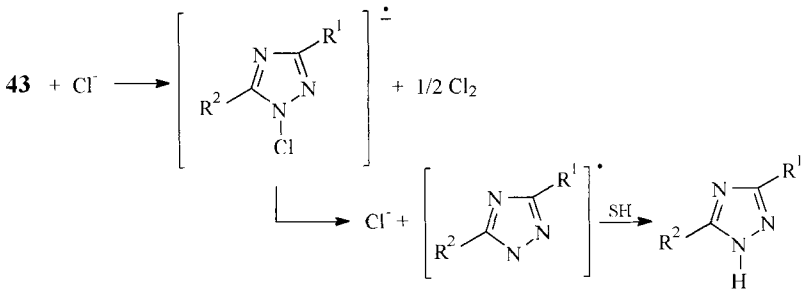
4. *Electrochemical Reduction of N-Chloro-1,2,4-triazoles*

Electrochemical reduction of a series of *N*-chloro-1,2,4-triazoles **43** at a platinum electrode in acetonitrile (90IZV2814; 91JEC499) is a two-electron process yielding the triazole anion and chloride ion (Scheme 44).

The values of the reduction potentials ($E_{1/2}$) increase with the electron-accepting properties of the ring (Table VI) and are in good correlation with the pK_a values of corresponding NH-triazoles (Eq. 1):



SCHEME 42



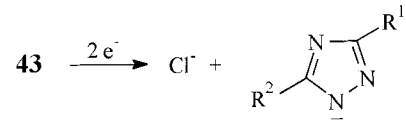
SCHEME 43

$$E_{1/2} = -(0.11 \pm 0.01)\, pK_a + (0.79 \pm 0.06) \qquad \text{(Eq. 1)}$$
$$n = 6;\ r = 0.981;\ s = 0.0519.$$

According to coulometric data, the amount of current for the complete exhaustion of the starting compound is in the range 0.45–1.3 F/mol depending on the accepting properties of the ring (Table VI). This effect arises from the competing chemical redox reaction of *N*-chlorotriazole with chloride ion, formed in the course of electrochemical reduction (see Section IV,B,3). The proportion of chemical transformation increases (and that of electrochemical transformation decreases) with the accumulation of electron-withdrawing substituents. This reflects the increase in oxidative ability of *N*-chlorotriazoles with an increase in the electron-withdrawing properties of the substituents. In general, it coincides with the experimental data on the effect of the accepting properties of the ring on the oxidative and halogenating activity of *N*-haloazoles.

5. *N-Haloazoles as Halogenating Agents*

Halogenation by *N*-haloazoles may take place by ionic (electrophilic) or free-radical mechanisms. An example of halogenation is the intermolecular N–C rearrangement of *N*-haloazoles (see Section IV,B,2). Almost all the studies involving *N*-haloazoles as halogenating agents were carried out using 1-chlorobenzotriazole **36a** (CBT), 1,3-dichlorotriazole **41a** (DCT), and 1,3,5-tribromotriazole **44** (TBT).



SCHEME 44

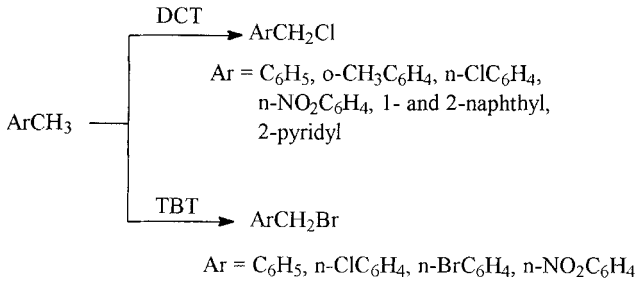
TABLE VI
REDUCTION POTENTIALS ($E_{1/2}$) AND COULOMBS (Q) CONSUMED DURING ELECTROREDUCTION OF *N*-CHLORO-1,2,4-TRIAZOLES (90IZV2814; 91JEC499)

Compound	$E_{1/2}$(v)	Q (F/mol)
1,3-Dichloro-1,2,4-triazole	−0.1	1.2
1-Chloro-3-nitro-5-methyl-1,2,4-triazole	−0.05	1.3
1-Chloro-3-nitro-1,2,4-triazole	0.1	0.75
1,3,5-Trichloro-1,2,4-triazole	0.2	0.8
1,5-Dichloro-3-nitro-1,2,4-triazole	0.4	0.45
1-Chloro-3-nitro-6-bromo-1,2,4-triazole	0.5	0.55

a. *Halogenation of Alkanes.* Reaction of DCT with hydrocarbons (*n*-pentane, *n*-hexane, *n*-heptane, *n*-octane, cyclohexane) in the presence of AIBN initiator at reflux yields a mixture of products of chlorination: 1-, 2-, and 3-chloropentanes, 1:18:24; 1-, 2-, and 3-chlorohexanes, 1:18:18; 1-, 2-, 3-, and 4-chloroheptanes, (1:18:18:18); 1-, 2-, 3-, and 4-chlorooctanes, (1:10:10:10); and chlorocyclohexane. Under the analogous conditions TBT reacts with these hydrocarbons to give 1-, 2-, and 3-bromohexanes (1:80:54); 1-, 2-, 3-, and 4-bromoheptanes (1:122:83:86); and bromocyclohexane. Halogenation proceeds by the radical mechanism (69ZC325). Cyclohexane is chlorinated to chlorocyclohexane under the action of CBT in the presence of benzoyl peroxide (72MI1).

b. *Halogenation of Alkylaromatic Compounds in the Alkyl Group.* Reaction of DCT with alkylarenes in the presence of AIBN or at reflux with an excess of the alkylarene gives the corresponding benzyl chlorides in high yields. *o*-Xylene reacts to form a mixture of *o*-chloromethyltoluene (55%) and *o*-xylilyne dichloride (45%). Ethylbenzene is chlorinated under these conditions in the methylene group to give 1-phenyl-1-chloroethane. Chlorination of analogous compounds containing electron-accepting substituents gives chlorides (*p*-chlorobenzyl and *p*-nitrobenzyl chlorides and 2-chloromethylpyridine) in lower yields (40–50%) (69ZC325). TBT reacts with alkylaromatic compounds more vigorously to give the corresponding benzylbromides. The yields of bromides with electron-withdrawing substituents in the ring (*p*-chloro, *p*-bromo, and *p*-nitrobenzyl bromides) reach 70–73% (69ZC325) (Scheme 45).

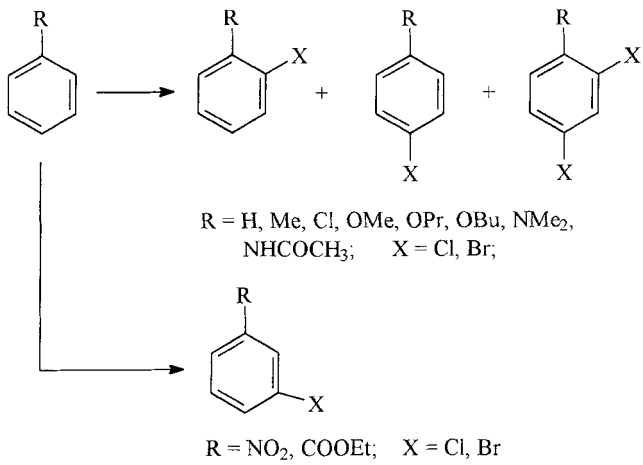
Chlorination of toluene with CBT at elevated temperature proceeds on the methyl group as well as on the ring. Together with benzyl chloride (40–50%) and a mixture of chlorotoluenes (8–20%) 1-benzylbenzotriazole (7%), benzotriazole (65%), and its hydrochloride (10%) are formed [69JCS(C)1478; 72MI2]. In this case radical as well as electrophilic halogenation takes place.



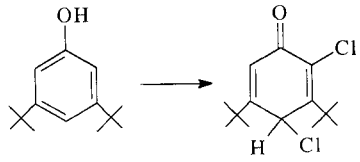
SCHEME 45

c. *Halogenation of Aromatic Compounds in the Ring.* Halogenation of aromatic compounds in the ring proceeds under the action of DCT or TBT in aqueous sulfuric acid or in organic solvents in the presence of aluminum chloride (69ZC325). The compounds with electron-donating substituents are halogenated even in the absence of catalysts. Alkyl phenolates are also halogenated in the ring in high yields (>80%); and the structure of isomers proves the electrophilic character of halogenation under these conditions. With the halogenation of compounds with electron-accepting substituents (R=NO_2, COOEt), the yields are somewhat lower. Chlorination of phenol with DCT leads to 2,3,6-trichlorophenol, *p*-cresol yields 2-chloro-*p*-cresol, anthranilic acid reacts to form the 5-chloro derivative, and naphthalene gives 1-chloronaphthalene (69ZC325) (Scheme 46).

Similar to DCT, CBT chlorinates aromatic compounds in the ring in methanol and methylene chloride in the presence or in the absence of aluminum chloride (72MI2). But contrary to DCT and TBT, compounds with



SCHEME 46



(60)

SCHEME 47

electron-withdrawing substituents do not react with CBT. On the whole, the yields of halogenated compounds in reactions with DCT are somewhat higher than those using CBT (72MI2).

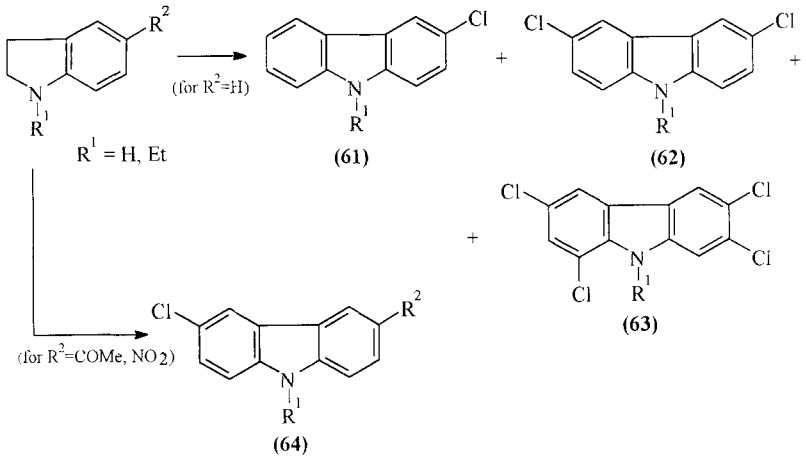
3,5-Di *tert*-butylphenol reacts with CBT to form 2,4-dichloro derivative **60** [86ZN(B)245] (Scheme 47).

Carbazole is chlorinated with CBT to form mono- and polychlorocarbazoles **61, 62, 63,** and **64** [71JCS(C)2775] (Scheme 48).

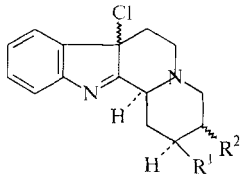
Chlorination of indole derivatives with CBT proceeds in position 3 of the indole ring [71JCS(C)2539; 74JOC69; 78HCA690]. Chlorination of indole alkaloids yields chloro derivatives **65, 66, 67,** and **68** (Fig. 4).

Chlorination of indoles with CBT is a radical process with intermediate formation of indole radical cation followed by its reaction with chlorine radical (82JOC4895) or chloride anion [91JCS(P2)1779] (Scheme 49).

Yields of 3-chloroindoles reach 90% while performing the reaction under nitrogen and decrease considerably in acetic acid in the presence of oxygen. Under these conditions together with chloroindoles the products of oxidation and dimerization are formed (Scheme 49).

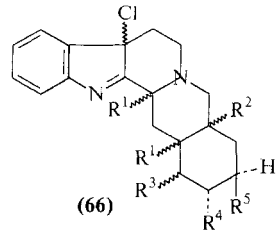


SCHEME 48



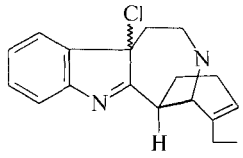
(65)

a. R^1=CH_2CN; R^2=β-Et
b. R^1=CH_2CHO; R^2=α-Et
c. R^1=CH(COOMe)CN; R^2=α-Et

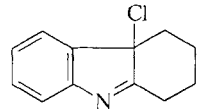


(66)

a. R^1=β-H; R^2=α-H; R^3=β-COOMe; R^4=OMe; R^5=3,4,5$(MeO)_3C_6H_2COO$
b. R^1=α-H; R^2=β-H; R^3=α-COOMe; R^4=OH; R^5=H



(67)



(68)

FIG. 4

N-Alkylperimidines are easily chlorinated with CBT (78KGS977, 78KGS1406). Chlorination proceeds according to the mechanism of electrophilic substitution and is governed by the amount of positive charge on the carbon atoms of the perimidine ring (78KGS1406).

1-Methylperimidine, depending on the excess of chlorinating agent, gives a mixture of monochloroperimidines **69** and **70** and di-, tri-, and tetrachloroperimidines **71–73** (Scheme 50).

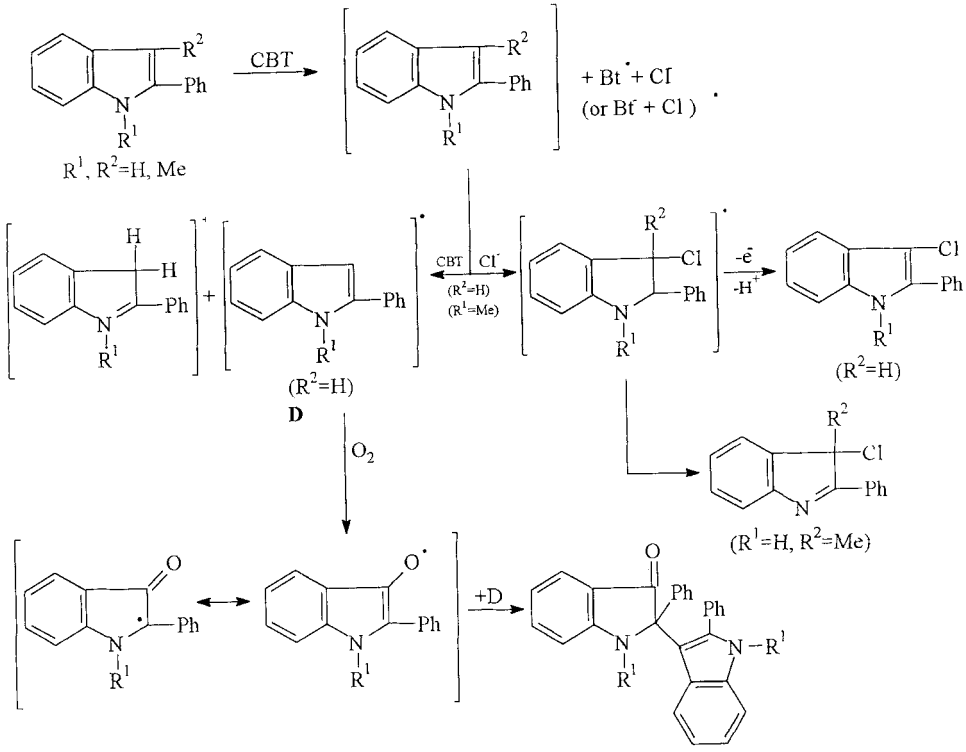
1-Methyl-6,7-dichloroperimidine gives a mixture of tri- and tetrachloroderivatives **72** and **73**. Chlorination of 1-isopropylperimidine leads to formation of 4,6,7-trichloroderivative **74** because of steric hindrance (78KGS977) (Fig. 5).

1,2-Dimethylperimidine reacts with CBT to form consecutively 4,9-dichloro-(**75**), 4,7,9-trichloro-(**76**), and 4,6,7,9-tetrachloro-(**77**) perimidines. (Fig. 6).

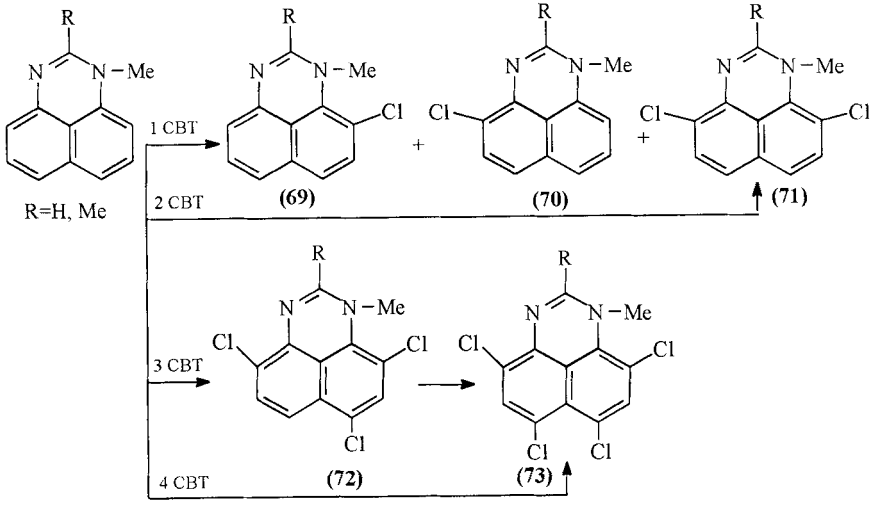
N-Unsubstituted perimidine under these conditions forms only tar. 1,3-Dimethylperimidone-2 under the action of CBT yields mono-(**78**), di-(**79**), tri-(**80**), and tetrachloroperimidones (**81**) (78KGS1406) (Scheme 51).

1,3-Dimethyl-2,3-dihydroperimidine under the action of CBT gives tar.

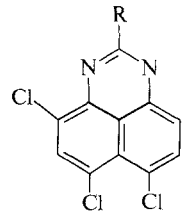
1,3-Dimethylperimidinium perchlorate reacts with 1 mole of CBT in acetonitrile to form a mixture of mono- and dichloro derivatives (**82** and **83**),



SCHEME 49



SCHEME 50



(74)

FIG. 5

and with an excess of CBT 6,7- and 4,9-dichloro derivatives (**84** and **85**) are formed in a 96:4 ratio (Fig. 7).

Derivatives of pyrazolo[1,5-a]benzimidazole are chlorinated with CBT at the pyrazole carbon atom, and substitution of the acetyl group with chlorine may take place (88KGS43) (Scheme 52).

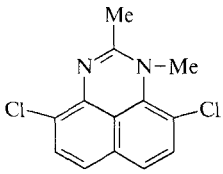
Analogous imidazoderivatives under the action of CBT undergo hetarylation at the methyl group of the imidazole moiety (80KGS1424) (Scheme 53).

d. *Halogenation of Ethers.* Ethers are halogenated with DCT in the α-position under mild conditions (0°) (69ZC325) (Scheme 54).

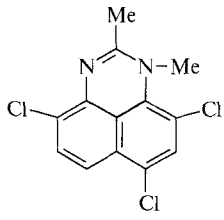
Reaction of ethers with CBT under more rigid conditions yields the products of oxidation and hetarylation. At room temperature CBT reacts with diethyl ether to form 1-ethoxyethylbenzotriazole (~5%) together with the chlorination products. In the reaction with tetrahydrofuran 1-(2-tetrahydrofuryl)benzotriazole is formed [69JCS(C)1474] (Scheme 55).

In this reaction an induction period is observed (~2 h); this decreases on UV irradiation. These observations prove the radical nature of the process (Scheme 56).

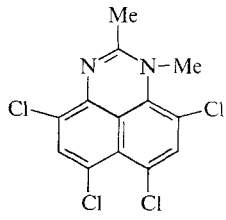
For the oxidative cleavage of ethers see Section IV,B,7,b.



(75)

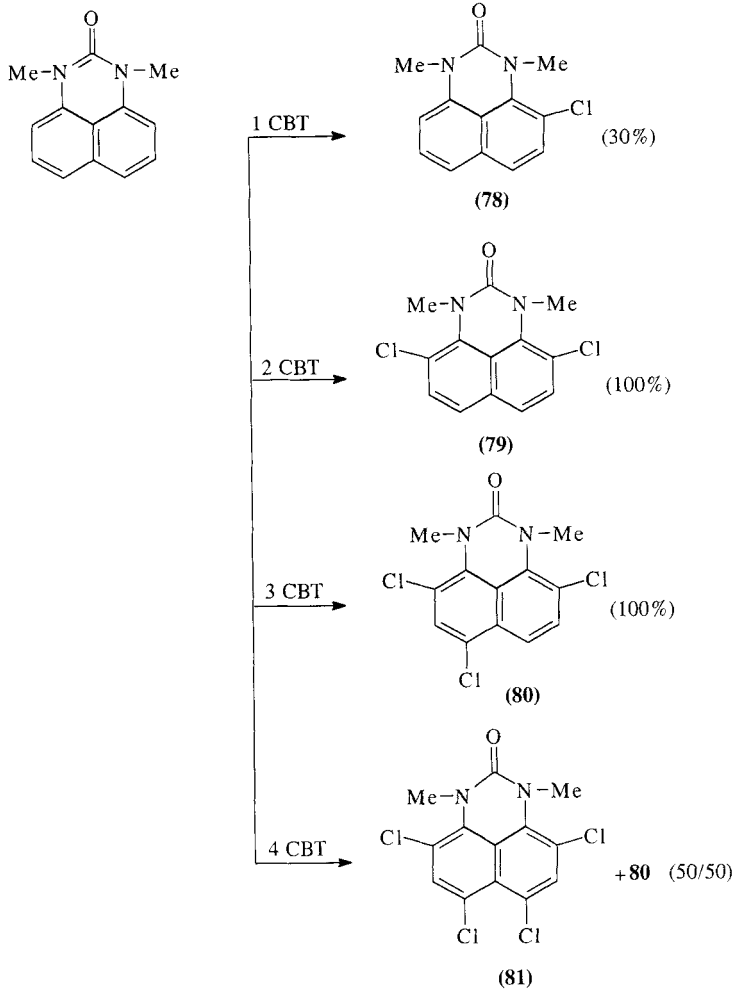


(76)

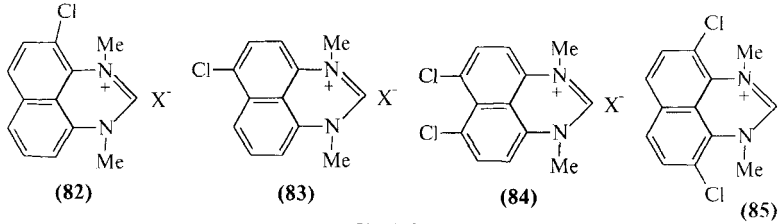


(77)

FIG. 6

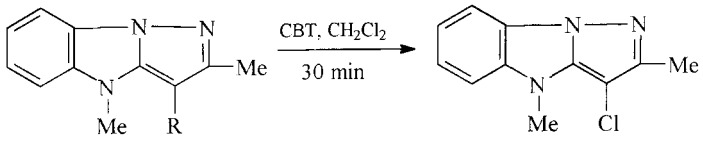


SCHEME 51



$X=ClO_4$

FIG. 7



R=H, $COCH_3$

SCHEME 52

e. *Halogenation of Aldehydes.* DCT reacts with benzaldehyde in carbon tetrachloride under UV irradiation to give benzoyl chloride (69ZC325) (Scheme 57).

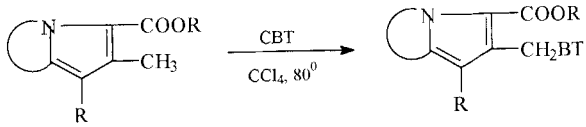
Kinetic studies of the chlorination of benzaldehyde with CBT in water–acetic acid mixtures [86IJC(A)478] show the reaction is the first order in CBT and zero order in substrate. Reaction rate increases with a decrease in pH and the addition of chloride ion (the first order by [Cl]). It is proposed that the chlorinating agent under these conditions is hypochlorous acid, which is formed from CBT as a result of protonation and subsequent hydrolysis. Its reaction with benzaldehyde is fast (Scheme 58).

DCT was used for chlorination of an imine prepared from benzaldehyde and benzylamine (69ZC325) (Scheme 59).

f. *Halogenation of Ketones and Compounds with an Active Methylene Group.* DCT and related compounds easily chlorinate acetone, acetophenone, cyclohexanone, and other compounds with an activated methylene group to form α-chloroderivatives (69ZC325) (Scheme 60).

1-Chloro- and 1-bromobenzotriazoles halogenate metal acetylacetonates in the γ-position with the preservation of the chelate structure or with the formation of complexes with the partial substitution of acetylacetone with benzotriazolyl moiety (96TMC457) (Scheme 61).

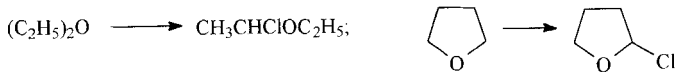
The chlorination of a series of substituted 1-methylpiperidin-4-ones **86** with CBT in aqueous acetic acid gave 3-chloroderivatives **87a–e** [88IJC(A)442]. The rate of the reaction was governed by a combination of



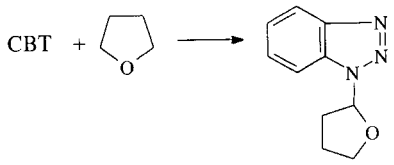
R=Me, Et BT=benzotriazol-1-yl

a-imidazo[2,1-a]isoquinoline
b-imidazo[1,2-a]pyridine
c-imidazo[1,2-a]benzimidazole

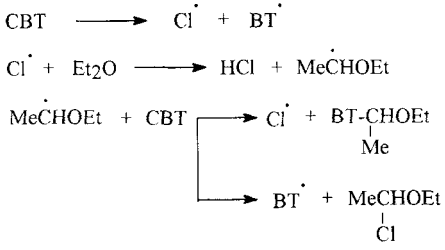
SCHEME 53

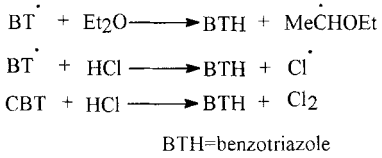


SCHEME 54



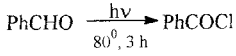
SCHEME 55



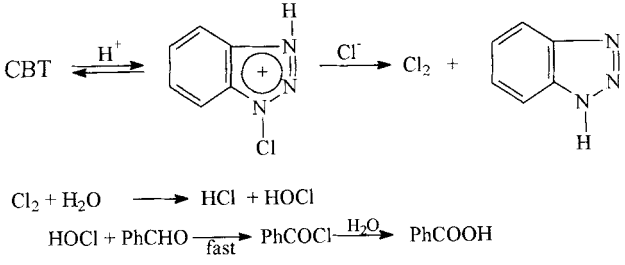


BTH=benzotriazole

SCHEME 56



SCHEME 57



SCHEME 58

$$PhCH{=}NCH_2Ph \xrightarrow{DCT,\ 90^0/1\ h} Ph\text{-}\underset{Cl}{\overset{|}{C}}\text{-}NHCH_2Ph$$

SCHEME 59

electronic and steric factors. *N*-Methyl-2,6-diphenylpiperidone **86a,** containing two equatorial hydrogens, is chlorinated faster than 3,5-dimethyl derivative **86b** and 3,3-dimethylpiperidone **86d**. Chlorination of tetraphenylpiperidone **86e** is the fastest process inspite of the steric hindrance created by the 3- and 5-phenyl groups (Scheme 62).

Thorough kinetics studies of the chlorination of aliphatic, alicyclic, and arylalkyl ketones with CBT were carried out by Indian workers (82PIA921). Kinetic measurements were performed using aqueous acetic acid and the addition of $HClO_4$ and NaCl. In the presence of mineral acid the reaction is first order in ketone and acid and zero order in CBT. A large kinetic isotopic effect was observed (for acetone k_H/k_D = 6.6). Addition of chloride ion causes some changes in the reaction order; they become first order in CBT, 0.6 in ketone, and 0.2 in chloride ion. The rate constant for chlorination of substituted acetophenones correlate with σ constants for substituents in the aryl ring (ρ is -0.57). On the basis of these data the mechanism in the absence and in the presence of chloride ion was developed.

In the absence of chloride ion the rate-determining stage is the enolization of ketone followed by rapid chlorination with CBT or with the reagents formed by its protonation. The last two processes are kinetically indistinguishable (Scheme 63).

The acidity of the medium influences the rate of enolization.

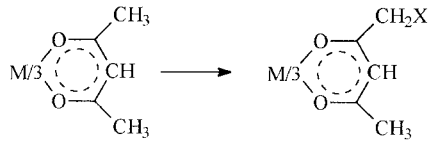
Observed changes in the reaction order in the presence of chloride ion show that it takes part in the formation of other halogenating agents by a reaction with CBT. The workers (82PIA921) consider that in this case a complex **C** is formed between protonated CBT and the chloride ion. This complex contributes the chlorination of the enolic form of a ketone (Scheme 64).

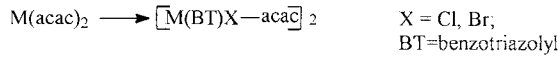
The negative value of ρ in the Hammet equation for aryl alkyl ketones arises from the presence of a positively charged reaction center in the transient state.

$$R^1CH_2R^2 \xrightarrow{DCT} R^1CHClR^2$$

a. R^1=H, R^2=COMe; b. R^1=H, R^2=COPh; c. R^1,R^2=$(CH_2)_4CO$
d. R^1=Me, R^2=CN; e. R^1=Ph, R^2=CN; f. R^1=CN, R^2=COOEt;
g. R^1=R^2=COOEt; R^1=R^2=COOH

SCHEME 60



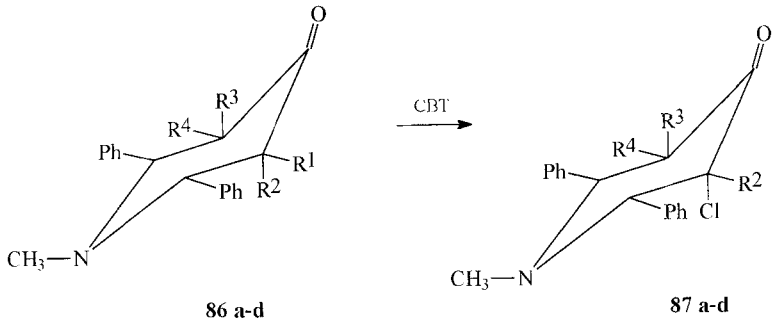


SCHEME 61

g. *α-Halogenation of Sulfoxides.* Reaction of CBT with sulfoxides in acetonitrile proceeds to form the products of chlorination of the α-carbon atom. In the case of methyl sulfoxides, α-chloromethyl derivatives are formed [72JCS(P1)1886, 72S259] (Scheme 65).

Reaction proceeds in the presence of pyridine, but in some cases the benzotriazole anion, formed in the course of the reaction, acts as a base. Reaction is stereospecific; halogenation of compounds with a prochiral α-carbon yields only one of two possible diastereoisomers. Chlorination of optically active sulfoxides takes place with preservation of configuration, but addition of silver ions causes the inversion of configuration at sulfur. The lability of hydrogen at the α-carbon atom does not considerably affect the direction of chlorination. On chlorination of benzyl methyl sulfoxide, benzyl chloromethyl and α-chlorobenzyl methyl derivatives are formed in approximately equal amounts (Scheme 66).

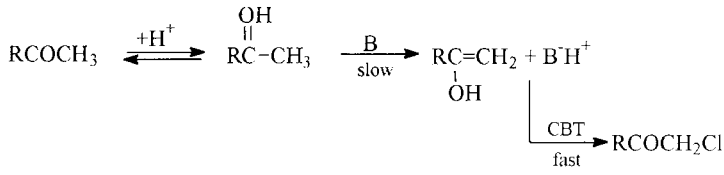
The kinetics of chlorination of arylmethyl and arylisopropyl sulfoxides with CBT in acetonitrile in the presence of pyridine show the reaction



86 a-d **87 a-d**

a. $R^1=R^2=R^3=R^4=H$; b. $R^1=R^3=H$; $R^2=R^4=Me$;
c. $R^1=R^2=R^3=H$; $R^4=Me$; d. $R^1=R^2=H$; $R^3=R^4=Me$;
e. $R^1=R^3=Ph$, $R^2=R^4=H$.

SCHEME 62



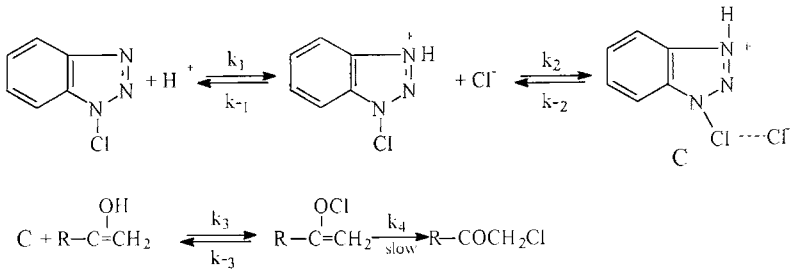
SCHEME 63

is second order (first order in sulfoxide and first order in CBT) [75JCS(P2)218]. The isotopic effect k_H/k_D was 3.1 for the chlorination of the methyl group and 7.0 for the isopropyl substituent. Rate constants correlate with the Hammet σ constants for substituents in the aryl ring (ρ is -4.35 for the chlorination of the methyl group and -3.71 for the isopropyl chain). The mechanism of chlorination includes the initial formation of an intermediate chloroxysulfonium salt, which reacts with a base (pyridine or benzotriazolyl anion) to remove the α-proton. This stage is followed by the migration of chlorine to the α-carbon atom (Scheme 67).

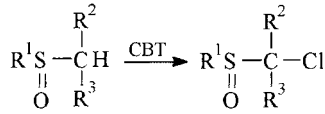
Migration of chlorine and deprotonation may proceed through a cyclic or bridged intermediate to preserve configuration. In the presence of silver nitrate coordination of Ag^+ by halogen or by the unshared electronic pair of oxygen or sulfur may cause the redistribution of charge in the intermediate, and the subsequent migration of halide to the carbon atom now proceeds with inversion of the configuration [72JCS(P1)1886] (Scheme 68).

Reaction of sulfoxides with CBT in a protic solvent (methanol) also proceeds through the formation of intermediate, which reacts with methanol to form the oxidation product (sulfone) (72S259) (Scheme 69).

h. *Chlorination of NH-Acids and Amines.* Succinimide and phthalimide react with DCT in aqueous acetic acid at 0°C to form *N*-chlorosuccinimide and *N*-chlorophthalimide in more than 80% yield (69ZC325) (Scheme 70).

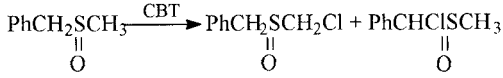


SCHEME 64

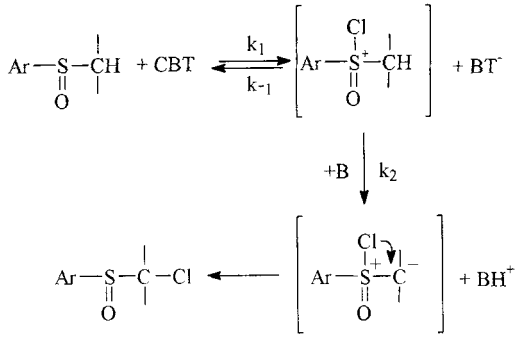


a. R^1=Ph, R^2=R^3=H; b. R^1=n-MeC_6H_4, R^2=R^3=H;
c. R^1=Ph, R^2=R^3=Me; d. R=Ph, R^2=H, R^3=Ph;
e. R^1=$PhCH_2$, R^2=R^3=H; f. R^1=PhCHD, R^2=R^3=H

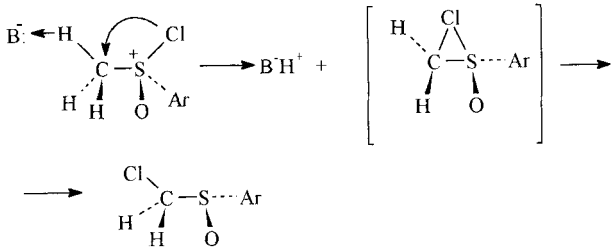
SCHEME 65



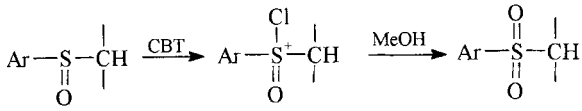
SCHEME 66



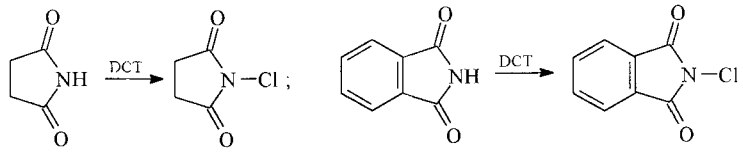
SCHEME 67



SCHEME 68



SCHEME 69



SCHEME 70

Phthalimide is chlorinated with CBT in benzene at reflux to form a chloro derivative in 44% yield (72MI1).

Primary amines, *tert*-butyl- and benzylamine, are chlorinated with CBT to the corresponding monochloroamines [76JCS(P1)741] (Scheme 71).

6. *Addition of N-Haloazoles to a C=C Bond*

Addition of *N*-haloazoles to a C=C bond may proceed by an electrophilic (ionic) as well as by a radical mechanism.

Reaction of DCT with styrene in polar protic solvents (water, acetic acid, and methanol) proceeds with the electrophilic addition of the halogen and the solvent moieties according to the Markovnikov rule. In carbon tetrachloride in the presence of an initiator (AIBN) addition of DCT and TBT to styrene proceeds to form anti-Markovnikov adducts and a small amount of 1,2-dihalo derivatives (69ZC325) (Scheme 72).

Reaction of DCT with cyclohexene in the presence of AIBN gives a mixture of *trans*-1-chloro-2-(3-chloro-1,2,4-triazol-1-yl)cyclohexane and 3-chlorocyclohexene-1 (69ZC325) (Scheme 73).

CBT adds to olefins to give a mixture of 1- and 2-(2-chloroalkyl)benzotriazoles with the 2-isomer [69JCS(C)1478] being the preferred formation. The rate of the reaction considerably depends on the nature of substituents in the double bond and decreases in the series (Fig. 8).

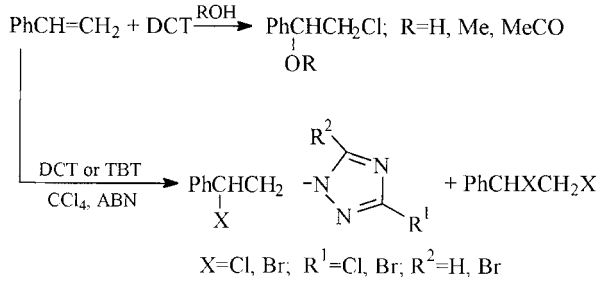
Addition of CBT proceeds according to the Markovnikov rule, as proved by the dehydrochlorination of the adducts (formation of 1,1-disubstituted olefins **88** and **89**) (Fig. 9).

1,3-Butadiene forms the products of 1,2- and of 1,4-addition in approximately equal amounts (Scheme 74).

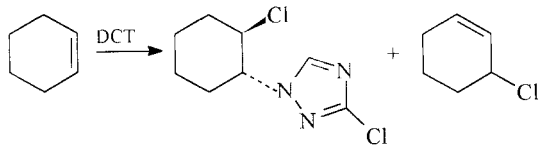
Addition of CBT to *cis*- and *trans*-butene-2 proceeds stereospecifically in the *trans* position to form corresponding *threo* and *erythro* isomers, which, after dehydrochlorination, yield the products **90** and **91,** respectively (Scheme 75).

R=t-Bu, $PhCH_2$

SCHEME 71



SCHEME 72



SCHEME 73

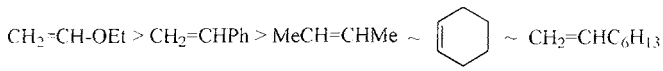


FIG. 8

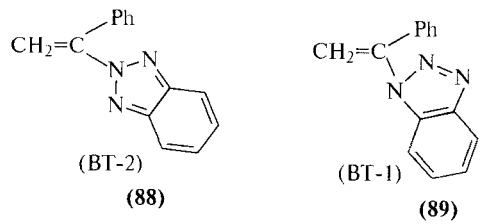
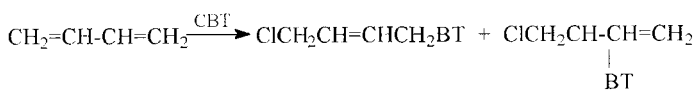
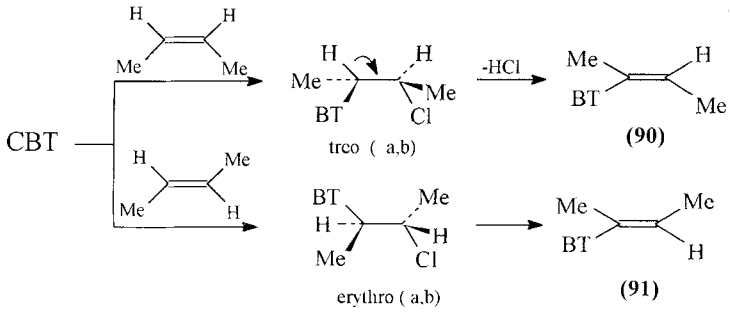


FIG. 9



SCHEME 74



SCHEME 75

Addition of CBT to cyclohexene in benzene and methylene chloride is also highly stereospecific; a mixture of *trans*-1-chloro-2-(benzotriazol-1-yl)- and *trans*-1-chloro-2-(benzotriazol-2-yl)cyclohexanes **92** and **93** in 25 and 40% yields, respectively, is formed (Fig. 10).

In acetic acid the main reaction product is 1-chloro-2-acetoxy derivative **94** (52%), while the other above-mentioned compounds are formed in 3 and 6% yields, respectively.

Orientation of the addition, stereospecificity, and the dependence of the reaction rate on the nature of the substituents, as well as the absence of an induction period, proves that this process is an electrophilic addition of Cl^+ followed by the nucleophilic attack of benzotriazolyl anion [69JCS(C)1478].

Ultraviolet radiation of a solution of CBT and cyclohexene in CH_2Cl_2 considerably changes the ratio of adducts **92** and **93** (40 and 20%, respectively), showing that a competing radical process takes place.

1-Bromobenzotriazole **38** and 1,4,5,6,7-pentachlorobenzotriazole **36b** react with cyclohexane more vigorously to form the corresponding adducts [78JCS(P1)909].

Reaction of CBT with alkenes was used as one convenient way to prepare *N*-vinylbenzotriazoles (obtained by dehydrochlorination of the initial products [90JCS(P1)485]). Thus, reaction of CBT with 5-trialkylsiloxypent-1-ene and with cyclopentene yielded a mixture of **95, 96,** and **97** (86T2985) (Fig. 11).

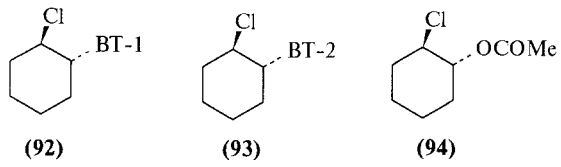


FIG. 10

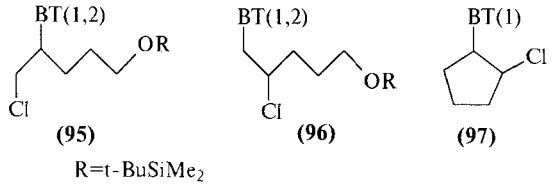


FIG. 11

2,3-Dihydro-4*H*-pyran adds *N*-chlorobenzotriazole to the double bond to form stereoisomeric derivatives (racemates) (71JHC1031) (Scheme 76).

A mixture of N-1 and N-2 benzotriazolyl derivatives **98** and **99** was obtained by the addition of CBT to ethyl vinyl ether (94T6005) (Scheme 77).

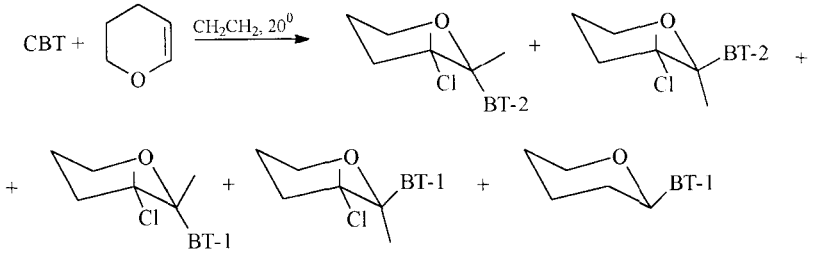
Treating 1-(morpholin-4-yl)cyclohexene with CBT in the presence of triethylamine yields bicyclo[3.1.0]hexane derivative **100** in 70% yield [94H(38)319]. Reaction proceeds through the formation of an intermediate chlorinated enamine and subsequent elimination of chlorine followed by the addition of benzotriazole (Scheme 78).

Treating symmetric tricyclic cyanines with CBT yields trichloro derivative **101,** in which the multiple bonds are preserved (86MI1) (Fig. 12).

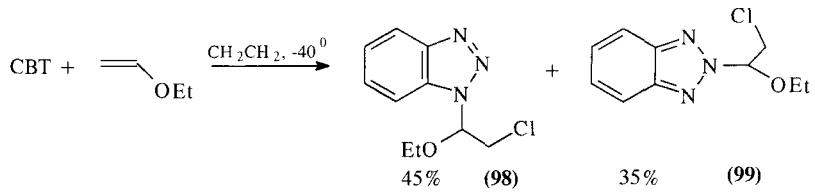
7. *N-Haloazoles as Oxidants*

N-Haloazoles, the sources of the positively charged halogens, may be used as soft oxidants of a series of organic substrates. For this purpose CBT and DCT are most widely used.

a. *Oxidation of Alcohols and α-Hydroxy Acids.* Benzyl alcohol is oxidized with DCT in organic solvents (tetrachloromethane or benzene–pyridine mixtures) to give benzaldehyde as the main product. Some benzoyl chloride is also formed by the chlorination of benzaldehyde (see Section IV,B,5) (69ZC325). TBT reacts with benzyl alcohol in benzene to



SCHEME 76



SCHEME 77

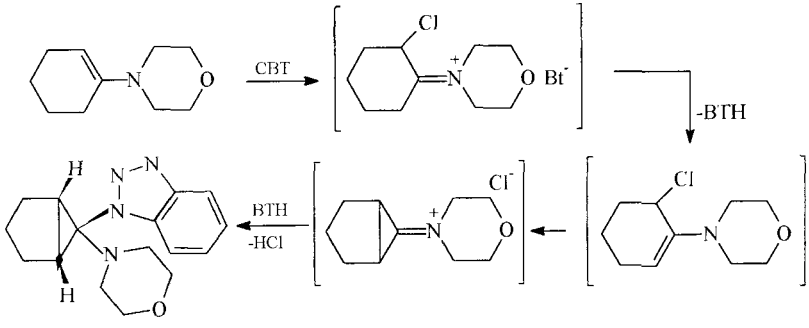
yield a mixture of benzaldehyde and benzoyl bromide, while in water benzaldehyde and benzoic acid are formed (69ZC325) (Scheme 79).

Oxidation of *n*-butanol with DCT yields a mixture of butyl butyrate and butanal. Isopropanol and cyclohexanol are oxidized with DCT and TBT to acetone and cyclohexanone, respectively. Under the same conditions α-hydroxypropanoic acid yields acetaldehyde (69ZC325) (Scheme 80).

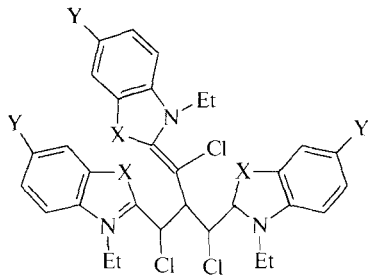
Analogous results were obtained on oxidation of benzyl alcohol, isopropanol, and cyclohexanol with CBT [68JCS(CC)1305; 69JCS(C)1474]. Methylphenylcarbinol and diphenylcarbinol under these conditions form acetophenone and benzophenone, respectively. Oxidation of alcohols in organic solvents is regarded as a radical chain process in which chlorine is the chain carrier [69JCS(C)1474] (Scheme 81).

Oxidation of cyclohexanol, phenylmethylcarbinol, and benzyl alkohol with *N*-bromobenzotriazole **38** proceeded to form cyclohexanone, acetophenone, and benzaldehyde. The yields in this case are lower than with CBT [78JCS(P1)909].

Cetyl alcohol is oxidized with CBT in methylene chloride to form palmitic aldehyde in 10% yield, but after the addition of 25% pyridine the yield of aldehyde reached 80–90% (72MI1). Cyclobutanone was obtained in 72% yield by oxidation of cyclobutanol with CBT (72JCED108).



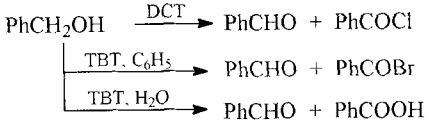
SCHEME 78



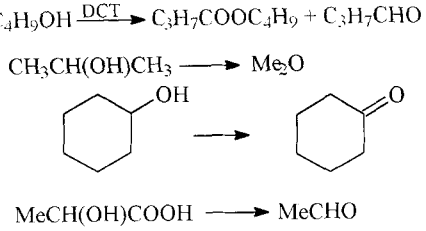
(101)

a. X=CMe_2, Y=H; b. X=S, Y=H; c. X=CMe_2, Y=Cl

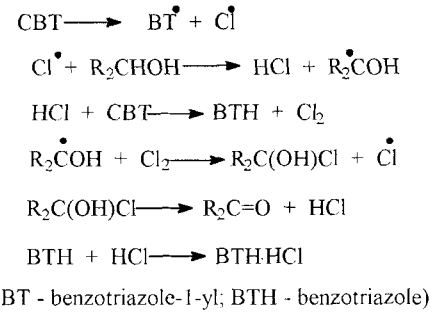
FIG. 12



SCHEME 79



SCHEME 80



(BT - benzotriazole-1-yl; BTH - benzotriazole)

SCHEME 81

Kinetic studies of oxidation of benzyl alcohols, phenylmethyl- and diphenylcarbinols, and α-hydroxyacids to the corresponding aldehydes and ketones were carried out by Indian workers [81JCS(B)898; 82IJC(B)42, 82IJC(B)1095; 83IJC(A)292; 87M583; 90MI1].

Oxidation was performed in aqueous acetic acid in the presence or absence of additives of strong mineral acids and chloride ions. CBT under these conditions may exist in an α-protonated form and act as an oxidant or it may give other oxidants with positively charged chlorine by reactions with the components of the reaction mixture.

Oxidation of benzyl alcohols and arylmethylcarbinols [82IJC(B)42] are first order in oxidant, alcohol, and proton concentrations unless some circumstances. The rate is described by Equation 2:

$$v = \frac{k_2 k[CBT][alcohol][H_3O^+]}{1 + k[H_3O^+]} \qquad \text{(Eq. 2)}$$

Equation (2) is in agreement with the scheme in which the acting oxidant is the protonated CBT or the products of its further transformations (H_2OCl^+, AcOCl, $AcOHCl^+$) (Scheme 82).

In the presence of chloride ions the reaction order in CBT changes from first to second (Eq. 3):

$$v = k[alcohol][CBT]^2[Cl^-]^{0.7} \qquad \text{(Eq. 3)}$$

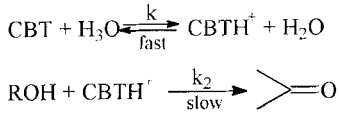
This fact may be explained by the formation of Cl_2O as the possible oxidant (Scheme 83).

An alternative explanation of (Eq. 3) involves the formation of molecular chlorine and its participation in oxidation with the simultaneous participation of the second molecule of CBT as the proton acceptor (Scheme 84).

In addition to CBT, benzotriazole and water may act as proton acceptors in the above-mentioned scheme.

The rate constants of oxidation of benzyl alcohols correlate with the σ-constants of substituents in the phenyl ring ($\rho = -4.5$). This fact is consistent with the carbocation character of the transient state.

Oxidation of diphenylcarbinol with CBT in aqueous acetic acid in the presence of perchloric acid yielded 4(7)-(chlorodiphenylmethyl)benzotriazole **102** instead of the expected benzophenone [81IJC(B)898]. This un-



SCHEME 82

$$2\ CBT + 2\ H_3O^+ + 2\ Cl^- \rightleftharpoons Cl_2O + 2\ HCl + 3\ H_2O + 2\ BTH$$

SCHEME 83

usual result arises from the formation of an electrophilic diphenylcarbocation, which attacks the benzotriazole ring (Scheme 85).

This scheme was confirmed by kinetic measurements showing the dependence of the reaction rate on the proton concentration and ionic strength and also by formation of diphenylcarbinol from bis(diphenylmethyl)ether (Scheme 86).

The rate of the reaction is described by Equation 4:

$$R = k[CBT][Ph_2CHOH][H^+]^2 \qquad \text{(Eq. 4)}$$

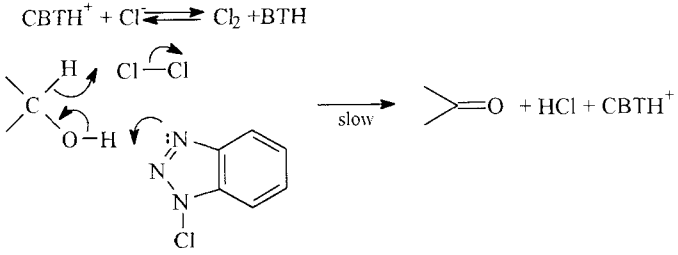
The dependence of the rate constant of this reaction on the ionic strength shows that two cations take part in the rate-limiting stage. The isotopic effect is insignificant (k_H/k_D 1.12). The reaction rate increases when electron-donating substituents are present in one of the phenyl rings of starting carbinol and decreases when it contains electron-accepting ones, but no Hammet correlation was observed. Addition of chloride ions to the reaction mixture causes the formation of chlorine, which also oxidizes diphenylcarbinol. As a result a mixture of 4(7)-substituted benzotriazole **102** and benzophenone is formed.

Benzophenone was obtained from diphenylcarbinol while using oxidants deactivated for electrophilic substitution, such *N*-chlorobenzotriazoles **36** and **37.**

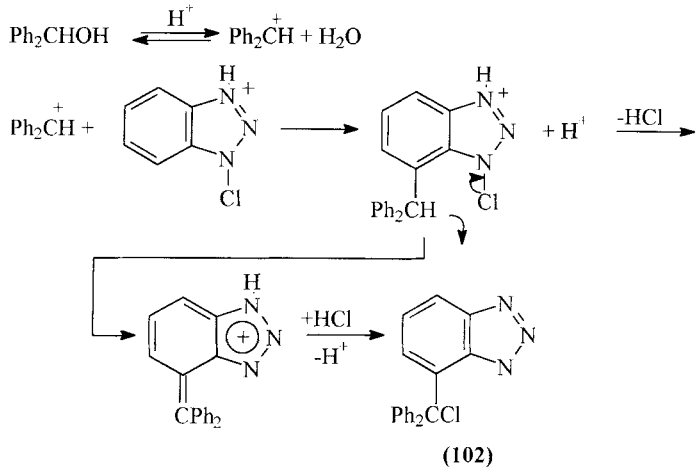
The kinetics of oxidation of fluorenol to fluorenone with CBT in aqueous acetic acid was studied [82IJC(B)1095] (Scheme 87).

At constant acidity a second-order reaction is observed (first order in each component) (Eq. 5). The rate constants exhibit a Hammet correlation ($\rho = -1.5$), and a small isotopic effect is observed (k_H/k_D 1.51):

$$R = k_2[\text{fluorenol}][CBT]. \qquad \text{(Eq. 5)}$$



SCHEME 84



(102)

SCHEME 85

These facts agree with the carbocation character of the transition state and the cleavage of the CH bond in the slow step of the reaction (Scheme 88).

The oxidation of cyclohexanol to cyclohexanone with CBT proceeds by an analogous mechanism (87M583).

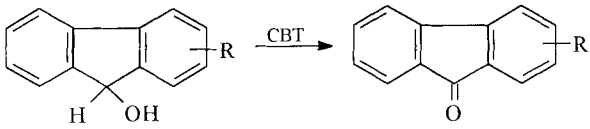
The kinetics of oxidative decaboxylation of mandelic acid, of substituted mandelic acids and of benzylic acid show the reaction is first order in both CBT and substrate, the reaction is pH dependent, and its rate increases on the addition of sodium chloride [83IJC(A)292] (Scheme 89). The rate-determining step is the reaction of mandelic acid with an oxidant (CBT or one of the products of its transformation).

An alternative mechanism of oxidation of such alcohols [82IJC(B)42], which also agrees with the kinetics of reaction, includes the participation of the carboxyl function. It includes the formation of an intermediate acyl hypochlorite and the subsequent intramolecular or intermolecular cleavage to the final products (Scheme 90).

The oxidation of a hydroxyl group with CBT in a highly strained polycyclic system **103** leading to formation of isoxazole ring and betaine structure **104** is described (73JOC407) (Scheme 91).

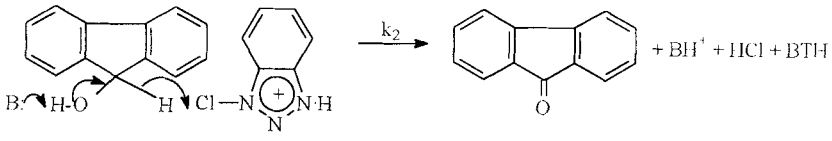
b. *Oxidative Cleavage of Ethers.* Ethers react with CBT in the presence of benzoyl peroxide on UV-irradiation or on heating to 50°C to form a mix-

SCHEME 86

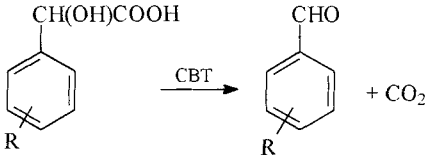


R=H, 2-Br, 2-Cl, 2-COOH, 2-NO_2, 3-Br

SCHEME 87



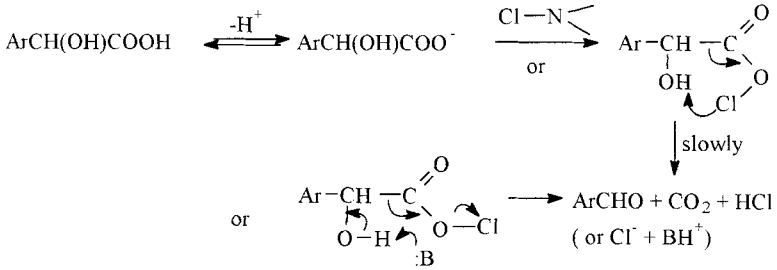
SCHEME 88



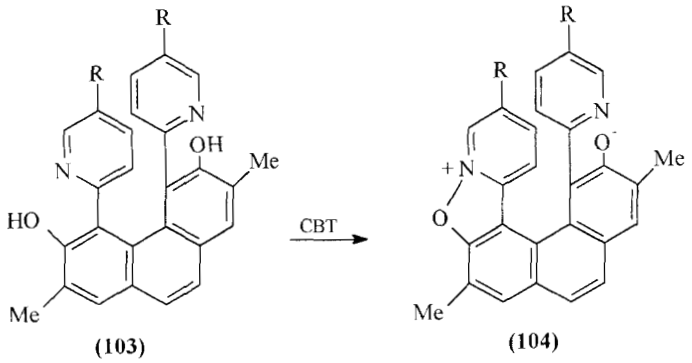
R=H, 4-Cl, 4-Br, 4-F, 2-OCH_3, 3-Cl, 3-Br, 4-Me

$Ph_2C(OH)COOH \xrightarrow{CBT} Ph_2CO + CO_2$

SCHEME 89



SCHEME 90



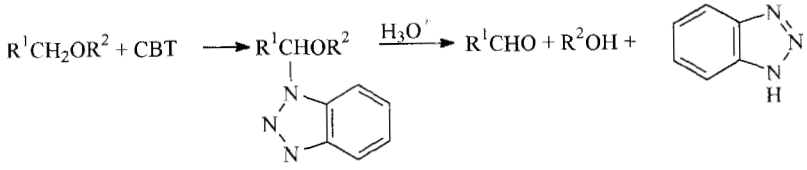
(103) (104)

SCHEME 91

ture of aldehydes and alcohols. Reaction proceeds through the intermediate formation of alkoxyalkenylbenzotriazoles (79AJC2787). The yields of aldehydes are 40–65% (Scheme 92).

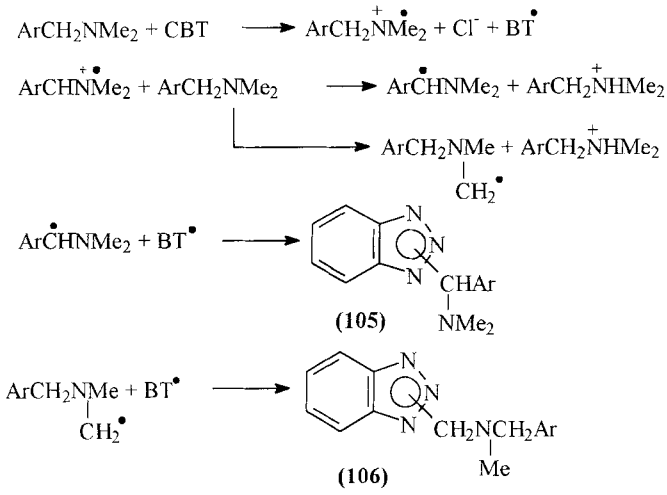
Dioxane under these conditions forms a mixture of ethylene glycol, glycolic aldehyde, and glyoxal, isolated as 2,4-dinitrophenylhydrazones (79AJC2787).

c. *Oxidation of Amines and Other Nitrogen-Containing Compounds.* The oxidation of *N,N*-dimethylbenzylamines with CBT is studied [76JCS (P1)741]. At the excess of amine the concentration of the reaction products containing active chlorine quickly decrease to 10–20% of the initial content of an oxidant and then diminish very slowly. The nature of the active chlorine product was not established, but it may be *N,N*-dimethylbenzylchloroammonium ion, though all attempts to obtain such chloroammonium derivatives failed. The reactions are generally second order (the first one in CBT and amine). The main products of oxidation are 1- and 2-(*N*-benzyl-*N*-aminomethyl)benzotriazoles **105** and 1- and 2-



R^1=Me, Pr, Ph; R^2=Et, Bu, Me; R^1R^2=-$(CH_2)_3$-, -$CH_2OCH_2CH_2$-

SCHEME 92



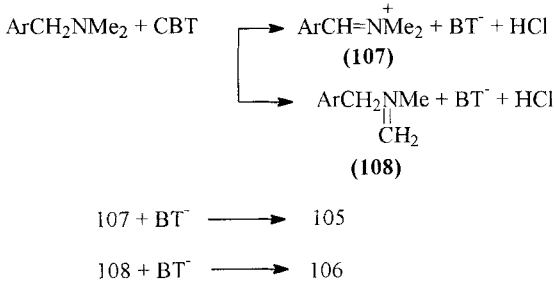
SCHEME 93

dimethylaminobenzylbenzotriazoles **106.** The mechanism of their formation, which coincides with the kinetic data, includes the initial formation of dimethylbenzylamine radical cation and its subsequent transformations (Scheme 93).

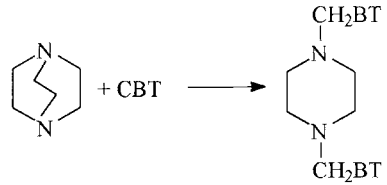
The alternative mechanism of formation of compounds **105** and **106,** which also agrees with the kinetic data, includes the formation of dimethyliminium ions **107** and **108** and subsequent addition of benzotriazolate anion (Scheme 94).

In the course of oxidation of 1,4-diazabicyclo[2.2.2]octane and *N,N,N′N′*-tetramethyl-1,4-diaminobenzene with CBT under the analogous conditions aminium radicals were traced by EPR.

The final product of oxidation of diazabicyclooctate is 1,4-bis(benzotriazolylmethyl)piperazine **109** [76JCS(P1)741] (Scheme 95).



SCHEME 94



(109)

SCHEME 95

Tri-*n*-butylamine is oxidized with DCT in water to form a mixture of dibutylamine and butanal (69Z325) (Scheme 96).

Kinetic studies of oxidation of α-amino acids (arginine, treonine, and glutamic acid) with CBT, leading to nitriles in 90% yields, were carried out in aqueous acetic acid in the presence and absence of perchloric acid and chloride ions [87JCS(P2)1569] (Scheme 97). Reaction rate decreases with the increase in the acidity of the medium and increases with the increase in the concentration of chloride ion. Under the studied conditions amino acids exist in a protonated form, and the complex formed by protonated CBT and the chloride ion acts as an oxidant. The mechanism of the reaction, which coincides with the kinetic data, includes initial slow chlorination of the amino group followed by subsequent formation of *N,N*-dichloramino derivatives and their transformations to the final reaction products (Scheme 98).

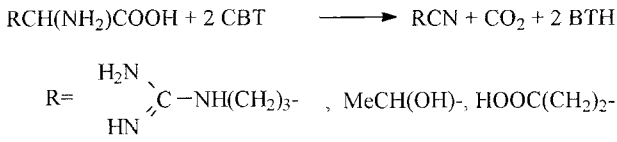
Oxidation of phenylalanine with DCT and TBT in water yields phenacetaldehyde (69ZC325) (Scheme 99).

Oxidation of *N,N'*-disubstituted thiourea and guanidines yields carbodiimides (74YGK727; 76YGK499) (Scheme 100).

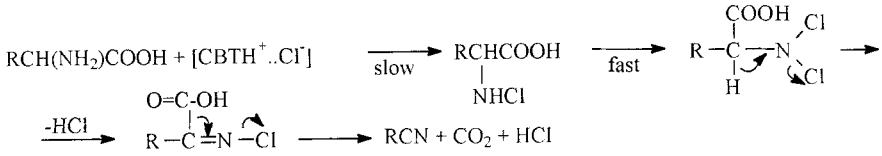
Oxidation of heterocyclic amino derivatives yields various reaction products depending on the structure of the amine. 4-Benzylamino-3-methyl-4*H*-1,2,4-triazole is oxidized with DCT in chloroform to give the azomethine derivative **110** (69ZC325). 1-Amino-4,5-diphenyl-1,2,3-triazole under the action of CBT forms diphenylacetylene; 2-aminobenzotriazole yields *cis, cis*-1,4-dicyanobuta-1,3-diene; and 1-aminobenzotriazole yields a mixture of chlorobenzene and *o*-dichlorobenzene. Oxidation of 1-aminobenzotriazole in the presence of tetraphenylcyclopentadienone leads to 1,2,3,4-tetraphenylnaphthalene via benzyne intermediate [68JCS(CC)1305; 69JCS(C)1474] (Scheme 101).

$$(C_4H_9)_3N \xrightarrow{DCT} (C_4H_9)_2NH + n\text{-}C_3H_7CHO$$

SCHEME 96



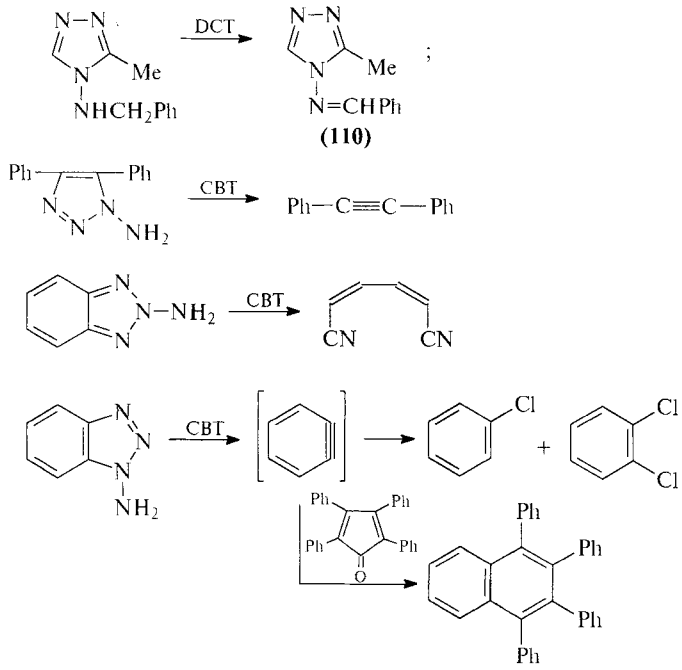
SCHEME 97



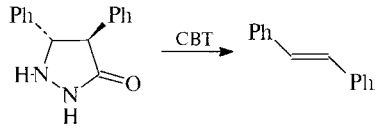
SCHEME 98

SCHEME 99

SCHEME 100



SCHEME 101



SCHEME 102

4,5-Diphenylpyrazolidin-3-one is oxidized with CBT to form *trans*-stilbene [69JCS(C)1474] (Scheme 102).

Oxidation of phenylhydroxylamine with CBT leads to nitrobenzene [69JCS(C)1474].

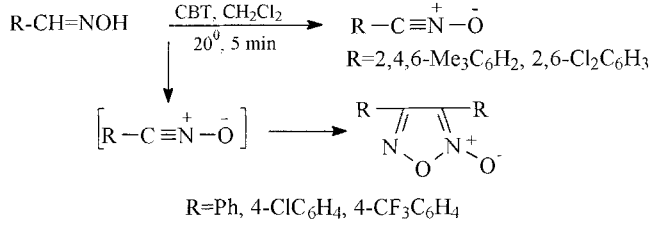
Aldoximes are easily oxidized with CBT under mild conditions to form nitrile oxides and furoxanes (90SC1373) (Scheme 103).

When the molecule of oxidated compound containes the oxime group and a C=C double bond in a configuration suitable for cycloaddition, a product with isoxazolone ring (**111**) is formed (90SC1373) (Scheme 104).

Kinetic studies of oxidation of acetophenone oximes with CBT in aqueous acetic acid were carried out (86MI1). The main reaction products are acetophenones. The scheme of oxidation, complying with the kinetic data and the effects of the acidity of the medium and the addition of chloride ions, proposes that the attack of positively charged chlorine on the oxime group nitrogen is the rate-limiting stage, followed by the fast transformation of the carbocation formed (Scheme 105).

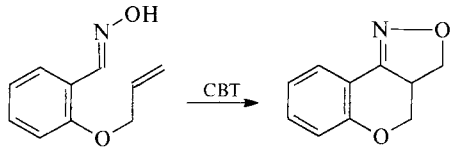
Hydrazo compounds are oxidized with DCT (79ZC325) or CBT [68JCS(CC)1305; 69JCS(C)1474] to form the corresponding azo derivatives (Scheme 106).

Reaction of CBT with benzophenohydrazone is complex [78JCS(P1)905]. Three moles of CBT per 1 mole of hydrazone are needed to complete the reaction. The first reaction product is diphenyldiazomethane, which was not traced in the reaction mixture because of the fast reaction with the second molecule of CBT leading to benzotriazolyl diphenyl methyl chloride **112.** The latter reacts with the third molecule of CBT either (a) through formation of triaryl carbocation and the subse-



R=Ph, 4-ClC_6H_4, 4-$CF_3C_6H_4$

SCHEME 103



(111)

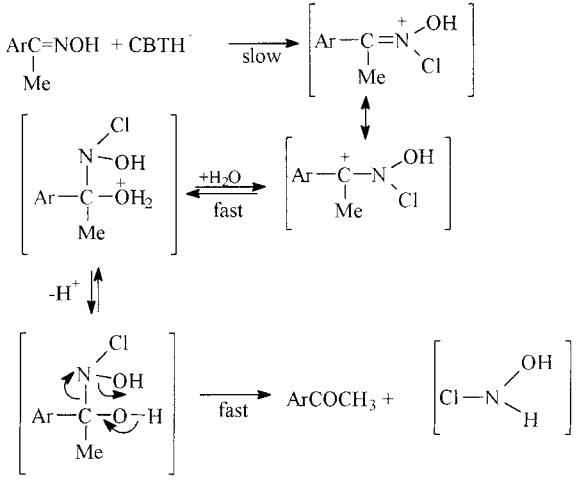
SCHEME 104

quent evolution of chlorine or (b) alkylation of CBT leading to a mixture of stable dibenzotriazolyl diphenyl methane **113** and unstable cyclohexadine **114** (Scheme 107).

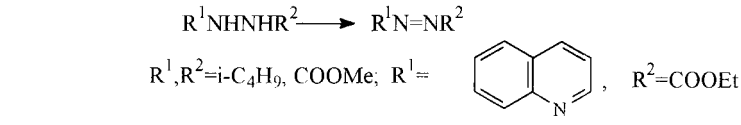
Formation of intermediate chloro derivative **112** was confirmed by its hydrolysis to benzophenone and alcoholysis to corresponding dimethyl ketal. Reaction of CBT with diazomethane resulting in formation of 1- and 2-chloromethylbenzotriazoles also confirms the proposed reaction scheme.

N-tert-Butyl-α-phenylnitrone **115** reacts under thermal or photochemical acivation to form a mixute of benzotriazole and its hydrochloride *Z*- and *E*-O-benzoyl oximes **116** and **117,** *tert*-butylbenzamide **118,** benzaldehyde, benzotriazolylphenyloxime **119,** and bis(*tert*-butyl)aminoxyl [96JCS(P2) 1297] (Scheme 108).

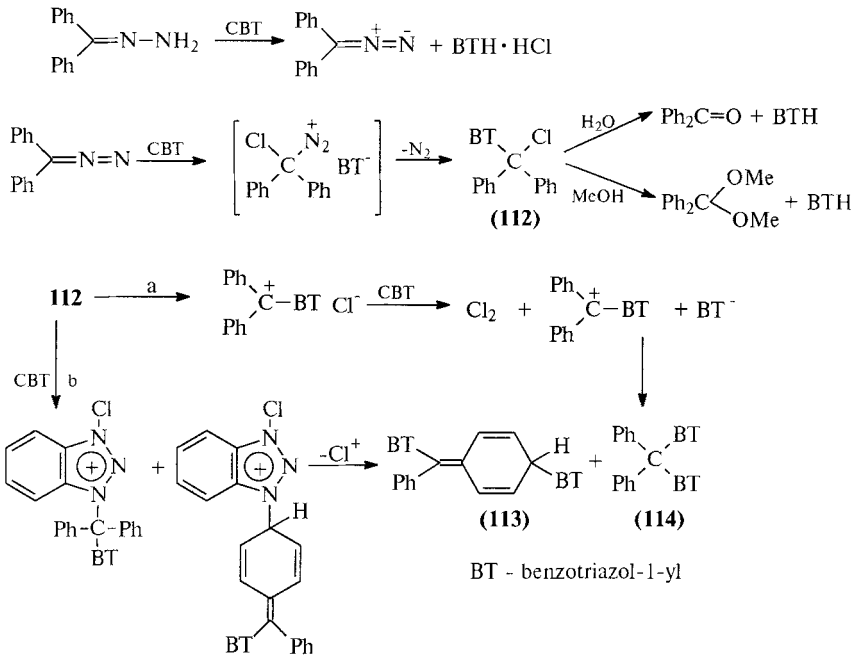
Reaction is catalyzed with benzotriazole. Performing the reaction in EPR spectrometer ampule permitted to trace isomeric benzotriazolyl spin adducts **120** and **121.** The latter transform to aminoxyl radical **122.** Under



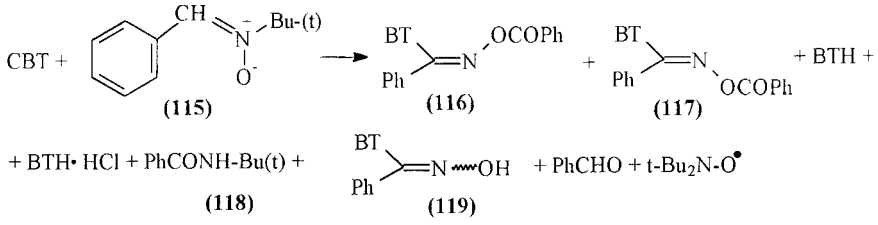
SCHEME 105



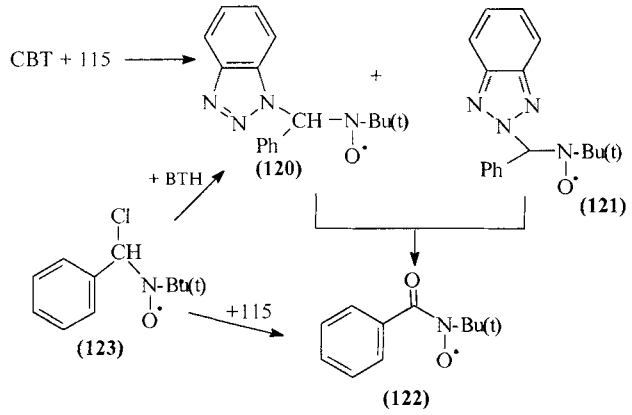
SCHEME 106



SCHEME 107



SCHEME 108



SCHEME 109

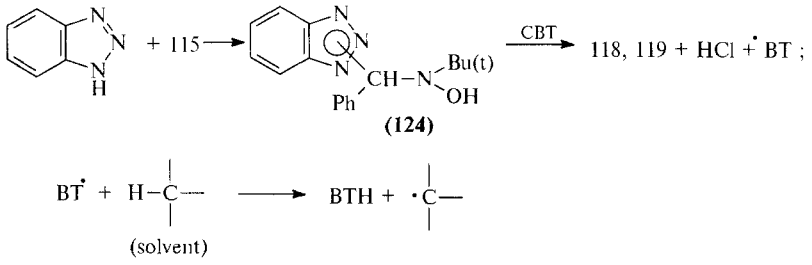
the large excess of CBT chlorine-containing adduct **123** is formed, which further converts to **120** and **122** (Scheme 109).

The mechanism of formation of **120** and **121** proposes the initiation of the process by the addition of benzotriazole (containing in trace amounts in CBT) to nitrone **115.** Obtained hydroxylamine derivative **124** is easily oxidized to give the radicals **120** and **121** (Scheme 110).

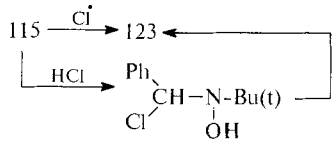
Under photochemical initiation the activated nitrone **115** reacts with CBT to form chloro-containing adduct **123.**

The other sources of adduct **123** may be the addition of Cl, formed under photochemical decomposition of CBT, to nitrone **115** or the addition of HCl to the same compound followed by oxidation of adduct (Scheme 111).

Transformation of adduct **123** to the radicals **120** and **121** may proceed through nucleophilic substitution of chlorine. Reaction of compound **123** with nitrone **115** may possibly yield acylaminoxime **122** and benzylidene derivatives **120** and **121,** which give rise to formation of benzaldehyde and amide **118.** Compounds **116, 117,** and **119** are formed by oxidation of adduct



SCHEME 110



SCHEME 111

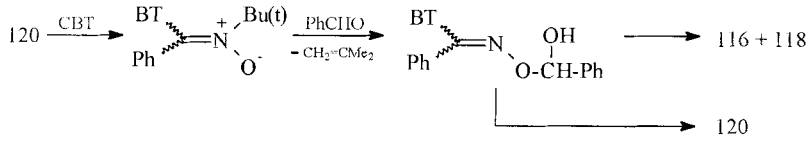
120 and the subsequent transformations of the obtained products (Scheme 112).

Formationof 2,3,5-triaryltetrazolium salts takes place in the reaction of 1,3,5-triarylformazans with CBT [94H(39)73]. Reaction obviously proceeds via intermediate *N*-chlorotriarylformazans (Scheme 113).

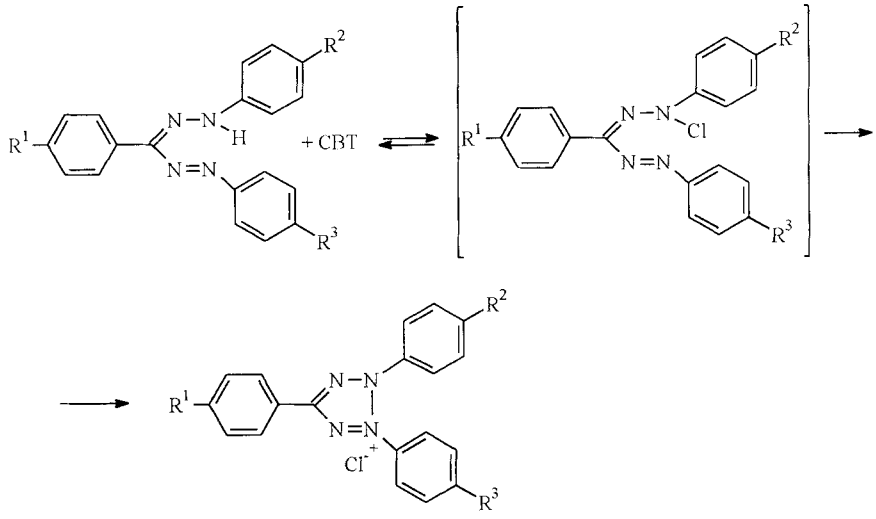
Oxidative amination of 2-phenylindole and 1-hydroxy-2-phenylindole with aromatic amines under the action of CBT [86JCS(P1)607] leads to 3-arylimino-3*H*-indoles. In the case of *N*-hydroxyindole the reaction is accompanied by the formation of isatogen and dimerization products [70AC(R)779; 86JCS(P1)607] (Scheme 114).

Comparison of the products obtained by oxidation with CBT and the results of electrochemical oxidation of a mixture of 2-phenylindole with arylamines permits speculation that amination probably proceeds through formation of nitrenium cation from *N*-chloramine [86JCS(P1)607] (Scheme 115).

d. *Oxidation of Halogen-Containing Compounds.* Reaction of CBT with iodocubane yields 2-cubylbenzotriazole (86TL6055) (Scheme 116). *N*-chloro, *N*-bromo-, and *N*-iodobenzotriazoles react with methyl iodide to give the products of mono- and dialkylation on the ring heteroatoms accompanied by formation of unsubstituted benzotriazole and iodine (95ZOR1231). In the reaction of CBT with methyl iodide formation of *N*-iodobenzotriazole **39** is observed in addition to the above-mentioned products. Compound **39** is consumed in subsequent transofrmations. Reaction rate decreases in the series: N–Cl->N–Br->N–J-benzotriazoles. Proposed reaction scheme incluces the ofrmation of an intermediate, containing trivalent iodine and its subsequent cleavage in several directions (Scheme 117).

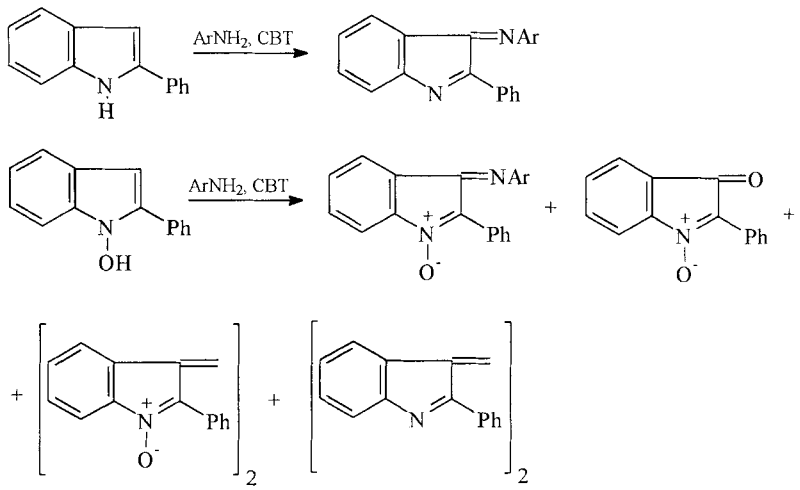


SCHEME 112



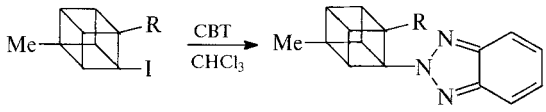
R^1=H, MeO, Cl, NO_2, Br;
R^2=H, NHAc;
R^3=H, Br, Me, NO_2, NHAc

SCHEME 113



SCHEME 114

SCHEME 115



SCHEME 116

N-chloro-1,2,4-triazole **43** reacts with methyl iodide in the same manner. Formation of iodine and a mixture of *N*-unsubstituted 1,2,4-triazoles, isomeric *N*-alkyltriazoles, *N*-iodotriazoles, 1,4-dimethyltriazolium salts, and the products of their further transformations is observed (94ZOR1398; 95ZOR113, 95ZOR1227). It is proposed that, similarly to *N*-halobenzotriazoles, formation of an intermediate trivalent iodine compound and its subsequent cleavage to the reaction products takes place (Scheme 118).

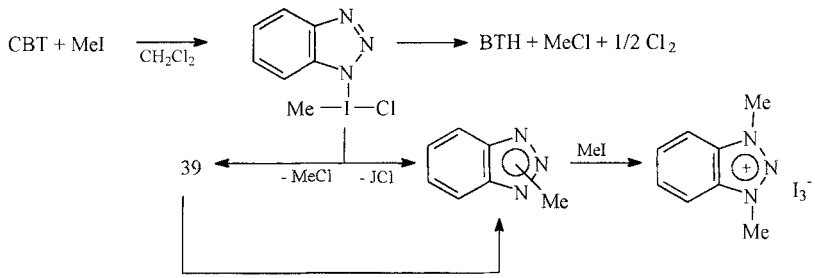
N-chloro-4-nitroimidazole **28** also enters the reaction with methyl iodide. In this case the main reaction product is 4-nitroimidazole (80% yield). Isomeric *N*-methylimidazoles and 1,4-dimethyl-4-nitroimidazolium triiodide are the minor products (5–6%) (97ZOR1847) (Scheme 119).

It is possible that an analogous redox mechanism takes place in the reaction of CBT with trityl chloride. The process results in the evolution of chlorine and the formation of 1-tritylbenzotriazole [78JCS(P1)905].

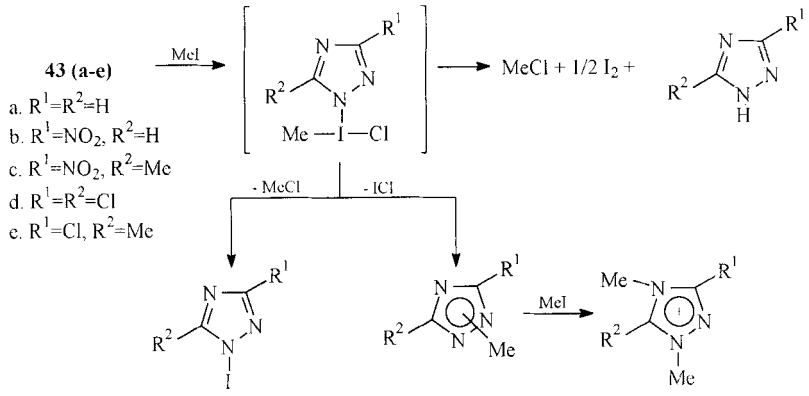
8. *Reaction of N-Haloazoles with Sulfur-Containing Compounds*

N-Haloazoles react with various sulfur-containing compounds such as oxidants and halogenating and hetarylating agents, converting sulfur to the higher degrees of oxidation. The reported data mainly deal with the reactions of CBT and only some examples concern DCT and TBT.

Thiophenol is oxidized with DCT or TBT to diphenyl disulfide. The latter reacts with DCT under more rigid conditions to give benzyl chloride. DCT oxidizes dibenzyl sulfide in methanol to dibenzyl sulfoxide (69ZC325) (Scheme 120).



SCHEME 117



SCHEME 118

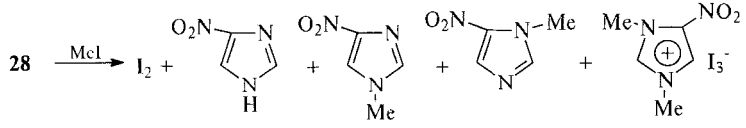
CBT oxidizes dialkyl sulfides to sulfoxides in high yields (70–98%) at −70°C in methanol or methylene chloride [69JCS(CC)365] (Scheme 121).

Contrary to DCT, reaction of CBT with diphenyl sulfide is not smooth. Benzyl chloride, dibenzyl disulfide, and some unidentified products were obtained. In the case of di-*tert*-butyl sulfide the formation of oxidation products was not observed [69JCS(CC)365].

Oxidation of unsymmetrical sulfides, such as **125,** to the corresponding optically active sulfoxides with CBT is high enantioselective, for example, in the synthesis of (*S*)-(-)-BOF-4272 **126a,** a xantine dehydrogenase inhibitor. Reaction proceeds in DMF in the presence of 4-cyanopyridine and a chiral alcohol (96TA2991) (Scheme 122).

Oxidation of **125** with *N*-bromobenzotriazole yielded sulfone **127.** Intermediate sulfonium nitrate **128** was isolated. Its thermal transformation to sulfoxide proceeds with preservation of configuration in compound **126a,** and alkaline hydrolysis causes the inversion (compound **126b**) (Scheme 123).

In some cases primary products of the reaction of dialkyl and diamino sulfides with CBT were traced in solutions. These ionic or covalent derivatives of tetracoordinate sulfur are convenient intermediates for the preparation of alkoxy- and aminosulfonium salts and sulfoxides [72TL501;



SCHEME 119

$$PhSH \xrightarrow[60^0,\ 1h]{DCT\ or\ TBT/CCl_4} PhSSPh \xrightarrow[80^0,\ 1h]{DCT} PhCH_2Cl$$

$$(PhCH_2)_2S \xrightarrow[-5^0]{DCT/MeOH} (PhCH_2)_2SO$$

SCHEME 120

75JCS(CC)868; 76BCJ601; 78JOC652; 80BCJ435; 82MI1] and SR_2 group carriers (78LA1754) (Scheme 124).

An example of the intramolecular formation of the S–N bond leading to thiazolidine-1-oxide on the treatment of aminoalkyl disulfides with CBT is presented (90JOC4156) (Scheme 125).

It is also reported (90TL1019) that oxidation of sulfide **129** with CBT results in the formation of dichlorobenzothiazocyne with hexa- (compound **130**) and penta-coordinated sulfur atom (compound **131**) (Scheme 126).

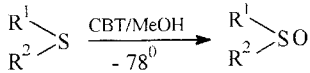
CBT reacts with sulfur to form bis(benzotriazolyl) sulfide in which benzotriazole is easily substituted by amine moieties (86ZOR100) (Scheme 127).

Reaction of CBT with thiol esters results in their cleavage and the formation of *N*-acetylbenzotriazole **132** (77CL1095). Sulfinamides **133** react with CBT in the presence of sodium benzoate to give benzotriazolylsulfinimides **134** [72JCS(CC)151] (Scheme 128).

Oxidation of *p*-toluenesulfinic acid with CBT yields tosylsulfonylbenzotriazole and tosyl chloride (83CPB1374) (Scheme 129).

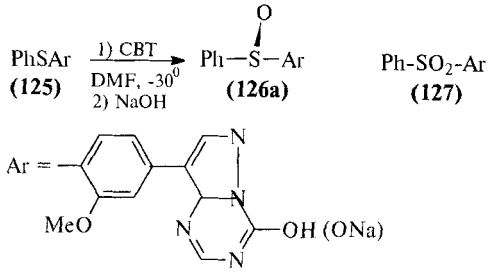
Oxidative cleavage of the C–S bond takes place while treating steroid thioacetals **135** with CBT. As a result ketones **136** are formed [71JCS(CC)750] (Scheme 130).

Reaction of penicillin esters **137** with CBT causes the cleavage of thiazolidine ring to form olefins **138** via intermediate benzotriazoyl derivatives. With excess CBT the olefins **138** are formed directly (72CCA423) (Scheme 131).

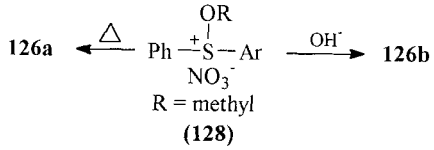


R^1=Me, R^2=Ph; R^1,R^2=$(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$;
R^1=Me, R^2=C_6H_4-NHCOMe (n)

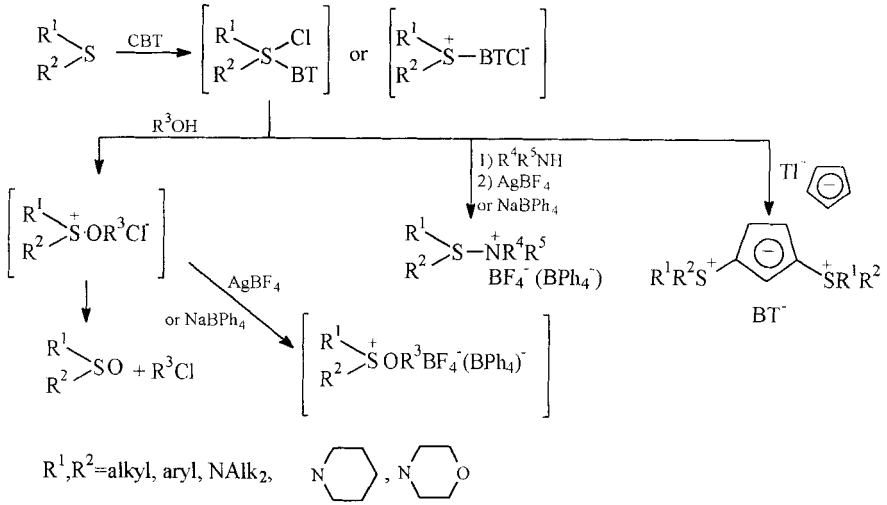
SCHEME 121



SCHEME 122



SCHEME 123

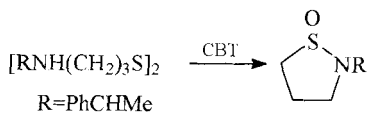


R^1,R^2=alkyl, aryl, $NAlk_2$,

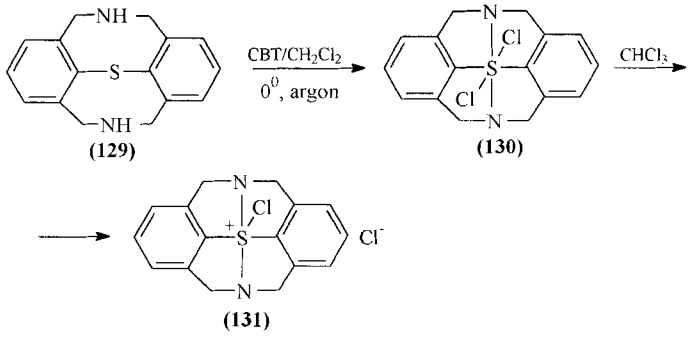
R^3=Me, Et, i-Pr, t-Bu, $MeCHC_6H_{13}$

R^4=Et, Ph, C_6H_{11}; R^5=H, Me, Et

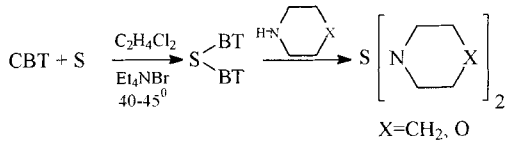
SCHEME 124



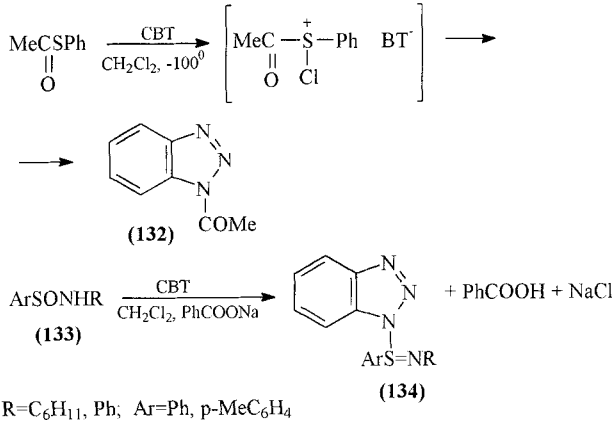
SCHEME 125



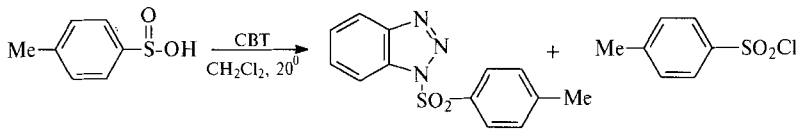
SCHEME 126



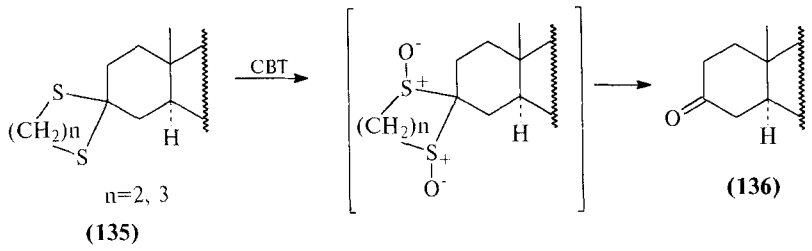
SCHEME 127



SCHEME 128



SCHEME 129



SCHEME 130

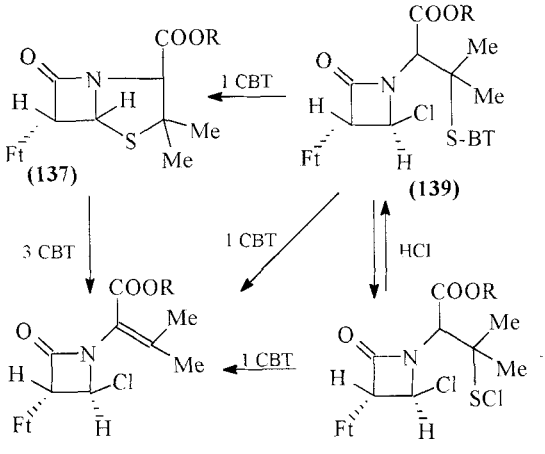
9. *Reaction of N-Chlorobenzotriazoles with Organoelement Compounds*

Arylselenium chloride reacts with CBT to form tetracoordinate selenium derivative **140** through the addition of chlorine and benzotriazolyl moiety (81ZOR529) (Scheme 132).

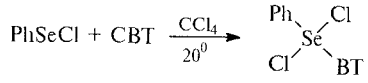
Diallyl selenide reacts with 2 moles of CBT to form bis(benzotriazol-1-yl)selenide (92TL2129). Reaction proceeds via the intermediate allyl benzotriazolyl selenide (Scheme 133).

Diaryl tellurides **141** react with CBT to form adducts **142** (79ICAL99) (Scheme 134).

Triphenyl(allyl)lead reacts with CBT to give the product of substitution of allyl group by benzotriazolyl moiety [79IJC(A)355] (Scheme 135).

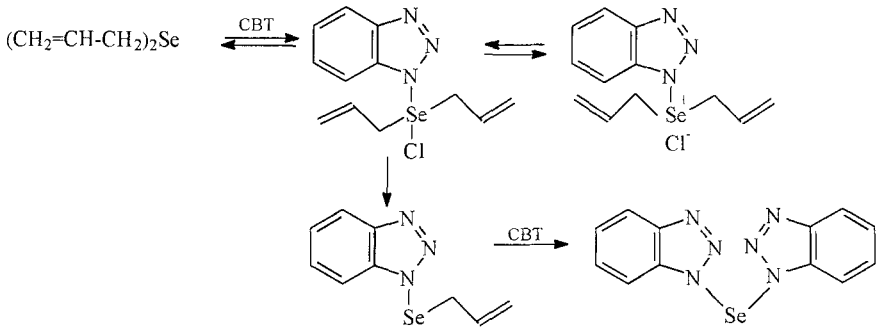


SCHEME 131

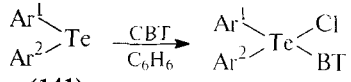


(140)

SCHEME 132



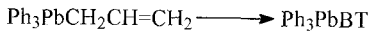
SCHEME 133



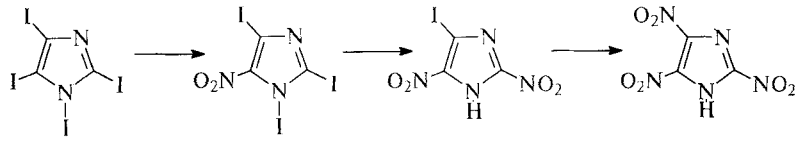
(141) **(142)**

Ar^1,Ar^2=Ph, p-$MeOC_6H_4$

SCHEME 134



SCHEME 135



SCHEME 136

10. *Miscellaneous*

Nitration of 1,2,4,5-tetraiodoimidazole proceeds as the consecutive substitution of iodine by nitro groups in positions 5, 2, and 4 and by hydrogen in position 1 (70KGS664; 78MI2) (Scheme 136).

1-Nitrobenzotriazole was obtained by treating CBT with trimethyl phosphite–silver nitrate complex (82S844) (Scheme 137).

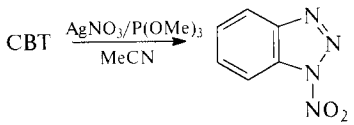
V. Applications

N-Haloazoles (especially *N*-chlorobenzotriazole) are widely used in organic synthesis as chlorinating agents and oxidants (see Section IV). Oxidative properties of CBT were used in analytical chemistry for quantitative determination of sulfur-containing compounds (90MI2; 91TAL1427), especially of cephalosporine, ampicillin (94MI1), and phenothiazine derivatives (94MI2).

Addition of 10^{-6}–10^{-5} mole of CBT in the electrolyte greatly changes the structure and morphology of layers in electrocrystallization of copper (87MI1).

Addition of CBT and other *N*-chloro compounds increases the stability of photographic materials on handling and protects them from reducing agents (73GP2162207; 78GP2725743; 80JPP79/63827, 80JPP79/95251; 85GP3413121; 87MIP1; 93JPP04/294345; 96JPP08/36249).

The use of CBT and other *N*-chloro compounds for preventing the destruction of cellulose and starch in the presence of spoilage enzymes such as cellulase and lipase is patented (91EP404374).



SCHEME 137

REFERENCES

10CB2243 H. Pauly, *Chem. Ber.* **43**, 2243 (1910).

55LA(593)179 R. A. Hüttel, H. Wagner, and P. Jochum, *Justus Liebigs Ann. Chem.* **593,** 179 (1955).

55LA(593)200 R. A. Hüttel, O. Schaefer, and P. Jochum, *Justus Liebigs Ann. Chem.* **593,** 200 (1955).

55LA(593)207 R. A. Hüttel and G. Welzel, *Justus Liebigs Ann. Chem.* **593,** 207 (1955).

56LA(598)186 R. A. Hüttel, O. Schaefer, and G. Welzel, *Justus Liebigs Ann. Chem.* **598,** 186 (1956).

63JCS2930 D. Harrison, J. T. Ralph, and A. C. B. Smith, *J. Chem. Soc.,* 2930 (1963).

64BCJ1018 T. Mikai and H. Tsuruta, *Bull. Chem. Soc. Jpn.* **37,** 1018 (1964).

65NEP6409386 Neth. Pat. Appl. 6,409,386 (1965) [*CA* **63,** 8382 (1965)].

67BP1123947 Br. Pat. 1,123,947 (1967) [*CA* **69,** 96734 (1968).

67CB2250 C. F. Kroeger and R. Mietchen, *Chem. Ber.* **100,** 2250 (1967).

67ZC184 R. Mietchen and C. F. Kroeger, *Z. Chem.* **7,** 184 (1967).

68FP1536979 Fr. Pat. 1,536,979 (1968) [*CA* **71,** 81347 (1969)].

68GP(E)60762 Ger. (East) Pat. 60,762 (1968) [*CA* **70,** 47462 (1969)].

68JCS(CC)1305 C. W. Reeds and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 1305 (1968).

68MIPI S. U. Pat. 203,693 (1968) [*CA* **70**, 11703 (1969)].

69JCS(C)1474 C. W. Reeds and R. C. Storr, *J. Chem. Soc.* C, 1474 (1969).

69JCS(C)1478 C. W. Reeds and R. C. Storr, *J. Chem. Soc.* C, 1478 (1969).

69JCS(CC)365 W. D. Kingsbury and C. R. Johnson, *J. Chem. Soc., Chem. Commun.,* 365 (1969).

69KGS1114 V. J. Grinstein and A. A. Strazdin, *Khim. Geterotsikl. Soedin.,* 1114 (1969).

69ZC300 R. Mietchen, H. U. Seipt, and C. F. Kroeger, *Z. Chem.* **9**, 300 (1969).

69ZC325 H. G. O. Becker, V. Eisenschmidt *et al.*, *Z. Chem.* **9,** 325 (1969).

70AC(R)779 L. Greci and G. Padovano, *Ann. Chim. (Roma)* **12,** 779 (1970).

70AHC(12)103 M. R. Grimmett, *Adv. Heterocycl. Chem.* **12,** 103 (1970).

70CB1949 H. Reimlinger, A. Noels, and J. Jadot, *Chem. Ber.* **103,** 1949 (1970).

70CRV639 P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.* **70,** 639 (1970).

70JOC2635 K. Witkowsky and R. K. Robins, *J. Org. Chem.* **35,** 2635 (1970).

70KGS558 L. I. Bagal and M. S. Pevzner, *Khim. Geterotsikl. Soedin.*, 558 (1970).

70KGS664 S. S. Novikov, L. J. Khmelnitskii, O.V. Lebedev, L. V. Epishina, and V. V. Sevast'yanova, *Khim. Geterotsikl. Soedin.*, 664 (1970).

70OMS1523 C. B. Thomas, *Org. Mass Spectrom.* **3,** 1523 (1970).

70ZC220 R. Mietchen, H. Albrecht, and E. Rachow, *Z. Chem* **10,** 220 (1970).

70ZN(B)934 K. H. Buechel, *Z. Naturforsch., B.* **25B,** 934 (1970).

70ZN(B)954 H. Roechling, E. Frasca, and K. H. Buechel, *Z. Naturforsch., B* **25B,** 954 (1970).

71CEN(49)30 H. B. Hopps, *Chem. Eng. News* **49,** 30 (1971).

71JCS(C)2539 K. V. Lichman, *J. Chem. Soc.* C, 2539 (1971).

71JCS(C)2775 P. M. Bowyer, D. H. Iles, and A. Ledwith, *J. Chem. Soc. C,* 2775 (1971).

71JCS(CC)750 P. R. Heaton, J. M. Midgley, and W. B. Whalley, *J. Chem. Soc., Chem. Commun.*, 750 (1971).

71JHC1031 G. Garsia-Muñoz, R. Madroñero, M. C. Saldana, M. Stud, and M. Rico, *J. Heterocycl. Chem.* **8,** 1031 (1971).

72CCA423 S. Kukolja and S. R. Lammert, *Croat. Chem. Acta* **44,** 423 (1972).

72JCED108 J. B. Siejr, *J. Chem. Eng. Data* **17,** 108 (1972).

72JCS(CC)151 F. Wudl, C. K. Brush, and T. B. K. Lee, *J. Chem. Soc., Chem. Commun.*, 151 (1972).

72JCS(P1)1886 M. Cinqini, S. Kolonna, R. Formazier, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1,* 1886 (1972).

72JPR923 H. G. O. Becker and R. Ebisch, *J. Prakt. Chem.* **314,** 923 (1972).

72MI1 H. Oelschlaeger and E. Ehlers, *Pharm. Acta Helv.* **47,** 1 (1972).

72MI2 W. J. Ferrell and K. C. Yao, *J. Lipid Res.* **13,** 23 (1972).

72S259 M. Cinquini and S. Kolonna, *Synthesis*, 259 (1972).

72TL501 C. R. Johnson, C. C. Bakon, and W. D. Kingsbury, *Tetrahedron Lett.*, 501 (1972).

73GP2162207 Ger. Offen 2,162,207 (1973) [*CA* **78,** 91067 (1973)].

73JOC407 D. L. Fields, T. H. Regan, and D. P. Maier, *J. Org. Chem.* **38,** 407 (1973).

74H(2)565 T. Hino, M. Endo, M. Tonozuka, and M. Nakagava, *Heterocycles* **2,** 565 (1974).

74JOC69 R. J. Owellen, *J. Org. Chem.* **39,** 69 (1974).

741YGK727 S. Furumoto, *Yuki Gosei Kagaku Kyokaishi* **32,** 727 (1974) [*CA* **82,** 125361 (1975)].

75BSF647 A. Bernardini, P. Viallefont, J. Daunis, M. L. Roumestant, and A. B. Sabatini, *Bull. Soc. Chim. Fr.*, 647 (1975).

75JCS(CC)482 M. De Rosa, *J. Chem. Soc., Chem. Commun.*, **482** (1975).

75JCS(CC)868 H. Minato, K. Okumas, and M. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 868 (1975).

75JCS(P2)218 D. Londini and A. Maia, *J. Chem. Soc., Perkin Trans. 2*, 218 (1975).

76BCJ3601 H. Minato, K. Okuma, and M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **49,** 3601 (1976).

76JCS(P1)741 J. R. L. Smith and J. C. Sadd, *J. Chem. Soc., Perkin Trans. 1*, 741 (1976).

76YGK499 S. Furumoto, *Yuki Gosei Kagaku Kyokaishi* **34,** 499 (1976) [*CA* **85,** 176906 (1976)].

76ZOB2576 V. N. Sheinker, L. G. Tishchenko, A. D. Garnovskii, and O. A. Osipov, *Zh. Obshch. Khim.* **46,** 2576 (1976).

77CL1095 H. Minato, K. Takeda, T. Miura, and M. Kobayashi, *Chem. Lett.*, 1095 (1977).

77CPB2350 T. Hino, M. Endo, M. Tonozuka, Y. Hashimoto, and M. Nakagawa, *Chem. Pharm. Bull.* **25**, 2350 (1977).

77ZOR2013 V. N. Sheinker, L. G. Tishchenko, A. D. Garnovskii, and O. A. Osipov, *Zh. Org. Khim.* **13,** 2013 (1977).

78GP2725743 Ger. Offen. 2,725,743 (1978) [*CA* **88,** 97386 (1978)].

78HCA690 J. R. Kutney, T. Honda, V. Joshua, N. G. Lewis, and B. R. Worth, *Helv. Chim. Acta* **61,** 690 (1978).

78JCS(P1)905 M. Heating, M. J. Sasse, and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 905 (1978).

78JCS(P1)909 M. J. Sasse and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 909 (1978).

78JOC652 H. Minata, K. Okuma, and M. Kobayashi, *J. Org. Chem.* **43,** 652 (1978).

78JOC2639 M. De Rosa and J. L. T. Alonso, *J. Org. Chem.* **43,** 2639 (1978).

78KGS977 V. V. Kuz'menko and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, 977 (1978).

78KGS1406 V. V. Kuz'menko and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, 1406 (1978).

78LA1754 K. Schlingensief and K. Hartke, *Liebigs Ann. Chem.*, 1754 (1978).

78MI1 M. J. Lebu, *Cah. Notes Doc.* **92,** 445 (1978) [*CA* **90,** 11461 (1979)].

78MI2 H. H. Cady, M. D. Coburn, B. W. Harris, and R. N. Rogers, Report 1977LA-6802-MS (1978) [*CA* **88,** 152497 (1978)].

79AJC2787 P. M. Pojer, *Aust. J. Chem.* **32,** 2787 (1979).

79ICAL99 T. N. Srivastava, R. S. Srivastava, and M. Singh, *Inorg. Chim. Acta* **33,** L99 (1979).

79IJC(A)355 S. N. Bhattacharya, P. Raj, and M. Singh, *Indian J. Chem., Sect. A* **17A,** 355 (1979).

79JCS(CC)419 T. Gallagher, M. J. Sasse, and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 419 (1979).

80BCJ435 K. Okuma, H. Minato, and M. Kobayashi, *Bull. Chem. Soc. Jpn.* **53,** 435 (1980).

80JOC76 J. F. Hansen, Y. J. Kim, L. N. Griswold, G. F. Hoelle, D. L. Taylor, and D. E. Vietti, *J. Org. Chem.* **45,** 76 (1980).

80JPP79/63827 Jpn. Pat. 79/63827 (1980) [*CA* **92,** 119686 (1980)].

80JPP79/95251 Jpn. Pat. 79/95251 (1980) [*CA* **92,** 13673 (1980)].

80KGS1424 V. V. Kuz'menko, T. A. Kuz'menko, and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 1424 (1980).

81IJC(B)898 A. Rangadurai, V. S. Srinivasan, and A. N. Venkatasubramanian, *Indian J. Chem., Sect. B* **20B,** 898 (1981).

81JCS(P1)403 J. de Mendoza, C. Millian, and P. Rull, *J. Chem. Soc., Perkin Trans. 1*, 403 (1981).

81JOC2054 M. De Rosa, L. Carbognani, and A. Febres, *J. Org. Chem.* **46,** 2054 (1981).

81MI1 P. C. Dvivedi and A. K. Banga, *Curr. Sci.* **50,** 213 (1981).

81ZOR529 N. J. Derkach and T. V. Lyapina, *Zh. Org. Khim.* **17,** 529 (1981).

82IJC(B)42 A. Rangadurai, V. Thiagarajan, and N. Venkatasubramanian, *Indian J. Chem., Sect. B* **21B,** 42 (1982).

82IJC(B)1095 P. Kuselan and N. Venkatasubramanian, *Indian J. Chem., Sect. B* **21B,** 1095 (1982).

82JOC1008 M. De Rosa, *J. Org. Chem.* **47,** 1008 (1982).

82JOC4895 C. Berti, L. Greci, R. Andruzzi, and A. Trazza, *J. Org. Chem.* **47,** 4895 (1982).

82MI1 K. Okuma, T. Doikawa, H. Ohta, and M. Kobayashi, *Fukuoka Daigaku Rigaki Shuho* **12,** 105 (1982) [*CA* **98,** 197702 (1983)].

82PIA921 P. C. Jayaraman, S. Sundaram, and M. Venkatasubramanyan, *Proc. Indian Acad. Sci.* **91** (Pt. 1), 921 (1982).

82S844 R. Ketari and A. Foucaud, *Synthesis*, 844 (1982).

83CPB1374 M. Nishikawa, Y. Inava, and M. Furukawa, *Chem. Pharm. Bull.* **31,** 1374 (1983).

83IJC(A)292 P. Cuselan and M. Venkatasubramanian, *Indian J. Chem., Sect. A* **22A,** 292 (1983).

83JOM(255)295 R. Soundararajan, S. Krishnamurthy, V. S. Srinivasan, and T. L. Balasubramanian, *J. Organomet. Chem.* **255,** 295 (1983).
84CHEC(4)1 C. W. Bird and G. W. H. Cheesman, *Compr. Heterocycl. Chem.* **4,** 1, (1984).
84CHEC(4)213 C. W. Bird and G. W. H. Cheesman, *Compre. Heterocycl Chem.* **4,** 213 (1984).
84CHEC(5)398 K. T. Potts, *Compre. Heterocycl. Chem.* **5,** 398 (1984).
84MI1 R. A. Machmoud, A. A. El Samahi, and M. M. Rafia, *J. Solution Chem.* **13,** 517 (1984).
85CB4588 A. Haas and C. Klare, *Chem. Ber.* **118,** 4588 (1985).
85GP3413121 Ger. Offen DE 3,413,121 (1985) [*CA* **102,** 176586 (1985)].
85JHC1631 A. Haas, C. Klare, and H. U. Kraechter, *J. Heterocycl. Chem.* **22,** 1631 (1985).
86H(24)1311 M. De Rosa, A. Cuenca, and M. R. Fernandez, *Heterocycles* **24,** 1311 (1986).
86IJC(A)478 K. Ganapathy, R. Gurumurthy, N. Mohan, and G. Sivagnanam, *Indian J. Chem., Sect. A*, **25A,** 478 (1986).
86JCS(P1)607 C. Berti, L. Greci, R. Andruzzi, and A. Trazza, *J. Chem. Soc., Perkin Trans. 1,* 607 (1986).
86MI1 R. Steiger, J. F. Reber, and H. Loeliger, *J. Imaging Sci.* **30,** 47 (1986).
86MI2 V. Sundasri and R. C. Devi, *Curr. Sci.* **55,** 850 (1986).
86T2985 P. A. Wender and C. B. Cooper, *Tetrahedron* **42,** 2985 (1986).
86TL6055 P. E. Eaton and G. T. Cunkle, *Tetrahedron Lett.* **27,** 6055 (1986).
86ZOR100 G. S. Borovikova, E. S. Levchenko, and E. J. Kaminskaya, *Zh. Org. Khim.* **22,** 100 (1986).
87JCS(P2)1569 R. C. Hiremath, S. M. Mayanna, and N. Venkatasubramanian, *J. Chem. Soc., Perkin Trans. 2,* 1569 (1987).
87JOC173 M. De Rosa, A. Quesada, P. Dodsworth, and D. J. Dodsworth, *J. Org. Chem.* **52,** 173 (1987).
87M583 K. Ganapathy, R. Gurumurthy, N. Mohan, and G. Sivagnanam, *Monatsh. Chem.* **118,** 583 (1987).
87MI1 P. B. Rotti and B. S. Sheshardi, *Indian J. Technol.* **25,** 266 (1987).
87MIP1 Pol. Pat. 126,285 (1987) [*CA* **107,** 31097 (1887)].
88IJC(A)442 R. Gurumurthy and E. Arunathi, *Indian J. Chem., Sect. A*, **27A,** 442 (1988).
88KGS43 T. A. Kuz'menko, V. V. Kuz'menko, and A. M. Simonov, *Khim Geterotsikl. Soedin.*, 43 (1988).
89JFC265 A. Haas and C. Klare, *J. Fluorine Chem.* **42,** 265 (1989).
90HOU586 R. Andree, J. Kluth, and W. Hanefeld, *Houben-Weyl Methoden Org. Chem.* **16a** (2), 586 (1990).
90IZV2814 V. V. Kozlov, M. E. Niyazimbetov, M. S. Pevzner, B. J. Ugrak, and V. A. Petrosyan., *Izv. Akad Nauk SSSR* 2814 (1990).
90JCS(P1)485 S. J. Barker and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 485 (1990).
90JOC4156 B. J. Wagner, J. T. Doe, and W. K. Musker, *J. Org. Chem.* **55,** 4156 (1990).
90MI1 R. C. Hiremath, S. M. Mayanna, and N. Venkatasubramanyan, *J. Sci. Ind. Res.* **49,** 122 (1990).
90MI2 C. Channedowde and S. M. Mayanna, *Mikrochim. Acta* **3,** 271 (1990).

90SC1373 J. N. Kim and E. K. Ryu, *Synth. Commun.* **20,** 1373 (1990).

90TL1019 H. Fujihara, N. Oi, T. Erata, and N. Furukawa, *Tetrahedron Lett.* **31,** 1019 (1990).

91EP404374 Eur. Pat. Appl. EP 404,374 (1991) [*CA* **115,** 88319 (1991)].

91JCS(P2)1779 P. Carloni, L. Eberson, L. Greci, P. Stipa, and G. Tosi, *J. Chem. Soc., Perkin Trans. 2*, 1779 (1991).

91JEC499 M. E. Niyazymbetov, V. A. Petrosyan, V. V. Kozlov, and M. S. Pevzner, *J. Electroanal. Chem.* **297,** 499 (1991).

91T7447 A. A. Gakh, S. F. Romanenko, B. I. Ugrak, and A. A. Fainzilberg, *Tetrahedron* **47,** 7447 (1991).

91TAL1427 C. C. Gowda and S. Mayanna, *Talanta* **38,** 1427 (1991).

92TL2129 M. D. Ryan and D. H. Harpp, *Tetrahedron Lett.* **33,** 2129 (1992).

93AHC(57)291 M. R. Grimmett, *Adv. Heterocycl. Chem.* **57,** 291 (1993).

93JPP04/29345 Jpn. Pat. 04/294,345 (1993) [*CA* **119,** 82791 (1993)].

93ZOR2326 T. P. Kofman, T. L. Uspenskaya, and M. S. Pevzner, *Zh. Org. Khim.* **29,** 2326 (1993).

94AHC(59)245 M. R. Grimmett, *Adv. Heterocycl. Chem.* **59,** 245 (1994).

94H(38)319 A. R. Katritzky, B. Galuszka, S. Rachwal, B. Mancheno, and P. J. Steel, *Heterocycles* **38,** 319 (1994).

94H(39)73 A. R. Katritzky, S. A. Belyakov, J. N. Lam, H. D. Durstand, and D. V. Karpenko, *Heterocycles* **39,** 73 (1974).

94MI1 M. L. Walash, S. Toubar, S. M. Achmed, and N. A. Zakhari, *Anal. Lett.* **27,** 2499 (1994).

94MI2 C. Channegowda and S. M. Mayanna, *Indian Drugs* **31,** 574 (1994) [*CA* **122,** 170340 (1994)].

94T6005 A. R. Katritzky, L. V. Ignatenko, X. Lan, M. Lang, and C. V. Stevens, *Tetrahedron.* **50,** 6005 (1994).

94ZOR1398 M. S. Pevzner, A. A. Kurenkov, and A. E. Trubitsin, *Zh. Org. Khim.* **30,** 1398 (1994).

95ZOR113 A. A. Kurenkov, M. S. Pevzner, and A. E. Trubitsin, *Zh. Org. Khim.* **31,** 113 (1995).

95ZOR1227 A. A. Kurenkov and M. S. Pevzner, *Zh. Org. Khim.* **31,** 1227 (1995).

95ZOR1231 A. A. Kurenkov and M. S. Pevzner, *Zh. Org. Khim.* **31,** 1231 (1995).

96JPP08/36249 Jpn. Pat. 08/36,249 (1996) [*CA* **124,** 302432 (1996)].

96JCS(P2)1297 P. Carloni, L. Eberson, L. Greci, P. Sgaralotto, and P. Stippa, *J. Chem. Soc., Perkin Trans. 2*, 1297 (1996).

96TA2991 M. Matsugi, K. Hashimoto, M. Imai, M. Fukuda, T. Furuta, J. Minamikava, and S. Otsuka, *Tetrahedron Asymmetry* **6,** 2991 (1996)

96TMC457 S. Thambidurai, K. Jeyasubramanian, and S. K. Ramaglingam, *Transition Met. Chem. (Weinheim. Ger.)* **21**, 457 (1996) [*CA* **125,** 315263 (1996)].

96UP1 M. S. Pevzner and V. V. Kozlov, unpublished results (1996).

97ZOR1847 E. A. Veretennikov and M. S. Pevzner, *Zh. Org. Khim.* **33** 1847 (1997).

98ZOR(ip) M. S. Pevzner and R. E. Trifonov, *Zh. Org. Khim.* **34** (in press).

Dimroth Rearrangement: Translocation of Heteroatoms in Heterocyclic Rings and Its Role in Ring Transformations of Heterocycles

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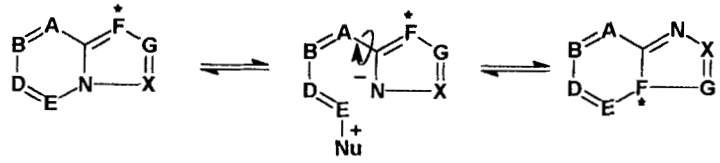
I. Introduction

The Dimroth rearrangement is an isomerization process whereby exo- and endocyclic heteroatoms are translocated on a heterocyclic ring. It is also considered to be amidine rearrangement. Unexpected products may form and the possible occurrence of rearrangement should be kept in mind whenever nucleophilic substitutions on those heterocycles are studied. There are only a few examples of retro-Dimroth rearrangement. This rearrangement may be classified into two main types, shown in Scheme 1. The translocation of heteroatoms in the first type can be between two rings of a fused system by three possible pathways: (a) an exocyclic heteroatom (**F***) of a ring becomes endocyclic, (b) a heteroatom in a five-membered ring (**N***) changes its location on the other ring, or (c) one of the heteroatoms of a five-membered ring (**G**) becomes a substituent on the other ring and the other two heteroatoms of the same ring become a part of another five-membered ring on cyclization. In (c) changes are promoted by the presence of an amino, hydroxy, or thiol group (X*H) at the *ortho* position of the heterocyclic ring; this group can then be incorporated to the new ring on recyclization after ring fission. In (b) the presence of a heteroatom within the five-membered ring at the exocyclic position of the other ring is a promoting factor for the rearrangement. The second major type involves the translocation of exo- and endocyclic heteroatoms on a single heterocyclic ring, an exoannular rearrangement, the mechanism of which has been studied since the early work on the subject. The rearrangement led to a translocation of the starred heteroatom.

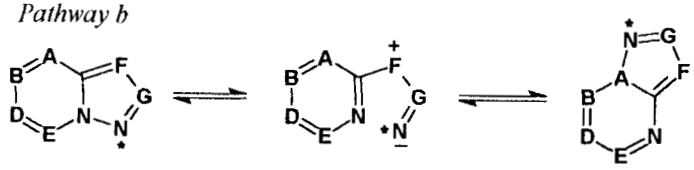
The Dimroth rearrangement can be catalyzed by alkali, acid, heat, or light. Several factors may influence such a rearrangement (80PAC1611). Thus, progressive azasubstitution in the ring leads to more facile nucleophilic attack at position 5 of the bicyclic system, an observation supported by MO calculations (71JHC643). Electron-withdrawing groups facilitate the ring-opening process. The pH of the solution affects the rate of rearrangement (77AJC2515). The thermodynamic stability of the rearranged bicyclic compound also affects the transformation.

Type 1: Translocation of heteroatoms within rings of fused systems

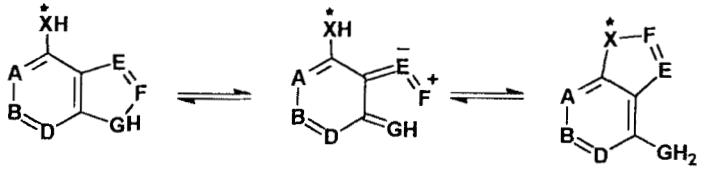
Pathway a



Pathway b



Pathway c



Type 2: Translocation of exo- and endocyclic heteroatoms in a heterocyclic ring

SCHEME 1

This rearrangement dates back to 1888 (1888CB867), but the second report was only in 1909 (09LA183). Subsequent reports (55JCS1858, 55JCS4035) recognized this rearrangement to be a general phenomenon in heterocyclic chemistry, particularly in the pyrimidine series. Since 1963, it has been termed the Dimroth rearrangement (63JCS1276). It should be noted that this rearrangement is different from the Dimroth reaction (71MI1). Two reviews have been published on the Dimroth rearrangement (68MI1; 69ZC241). Examples of the second type of rearrangement (Scheme 1) were at the beginning much more numerous than the first. Re-

views also address particular examples of heterocycles (74AHC33) such as aminoazoles (84CHEC94) and 1,2,3- and 1,2,4-triazolo[x,y-*z*]pyrimidines [98AHC(57), 99AHC(127)]. This chapter reviews the subject from 1967 to 1995 (*Chemical Abstracts* volumes **67** through **123**). However, some older references are also given to emphasize the scope of the subject.

This chapter is divided into two main sections. The first includes the translocation of heteroatoms between rings of fused systems and the second includes the translocation of exo- and endocyclic heteroatoms within ring types 1 and 2 in Scheme 1. Each section is further divided according to the number and arrangement of heteroatoms in the ring.

II. Translocation of Heteroatoms within Rings of Fused Systems

This rearrangement is of potential value for the improved synthesis of heterocyclic compounds, which may otherwise be synthesized by more elaborate ways. It was considered in an earlier review (68MI1) as a possible Dimroth rearrangement, but then was further reported as a true Dimroth rearrangement. The fused heterocycles that undergo such translocation of heteroatoms are characterized by having a five-membered heterocyclic ring as one of its components. This rearrangement is classified according to the nature of the five-membered ring and whether it contains two or three heteroatoms and then subdivided according to the relative arrangement of these atoms. Only a relatively few examples are reported for pyrazolo and imidazo heterocycles compared to their 1,2,4-triazolo analogs (80PAC1611).

Dimroth rearrangement of the N-atoms in the five-membered ring of several polyazaindolizines [59JOC787; 60JCS1829; 63JCS1276, 63JCS1284, 63JCS56412; 66CB2237, 66JCS2038, 66JOC265; 68JHC485, 68MI1; 69BSF2492, 69BSF3670; 70JCS(CC)1524, 70JHC1019] depends on covalent hydration that occurs at positions 5, 7 (65JA1980), or 8 [70JCS(CC)1524]. Calculation of the electron densities of a number of pertinent polyazaindolizine systems allows their classification according to their electron densities at position 5. Thus, an aza group at positions 6 or 8 renders the 5-position more electrophilic, while at position 7 it has no effect. Moreover, an extra N-atom at position 2 decreases the π-electron density at position 5 more than an N-atom at position 3 (71JHC643).

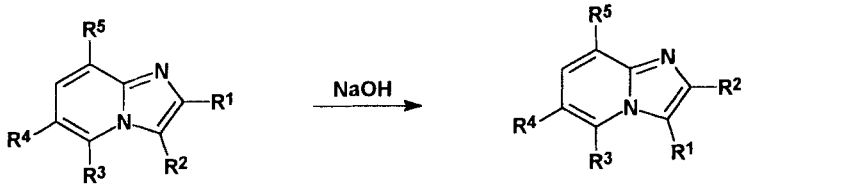
A. Rearrangement of Imidazo Heterocycles

2-Phenylimidazo[1,2-*a*]pyridine did not rearrange to 3-phenylimidazo [1,2-*a*]pyridine under alkaline conditions (60JA3147). However, when the

imidazo[1,2-*a*]pyridine was activated by a nitro group at positions 6 or 8 as in **1** or **2,** Dimroth rearrangements take place in aqueous basic media to give **4** and **5,** respectively (73JHC755). Similarly, imidazopyridinylmethylphosphonium salt **6** was obtained on rearrangement of **3** (75LA1934) (Scheme 2).

A method for activation is the introduction of an additional nitrogen atom into the six-membered ring, as, for example, in the imidazo[1,2-*a*]pyrazine, imidazo[1,2-*a*]pyrimidine (**7**), or imidazo[1,2-*c*]pyrimidine (**10**) systems. Because of its electron-withdrawing property, the extra aza group of the last two systems activates the 5-position for base-catalyzed Dimroth rearrangement.

When 3-methylimidazo[1,2-*a*]pyrimidine (**7;** R=Me, R^1=R^2=R^3=H) was heated in aqueous 1% sodium hydroxide, it rearranged to 2-methylimidazo[1,2-*a*]pyrimidine (**9;** R=Me, R^1=R^2=R^3=H). Similarly 3,5-dimethyl- and 3,7-dimethylimidazo[1,2-*a*]pyrimidine rearranged to the corresponding isomer **9.** On the other hand, 3-methyl- or 2-methylimidazo[1,2-*a*]pyrazines failed to rearrange under the same conditions. 3-Methylimidazo[1,2-*c*]pyrimidine (**10;** R^1=R^3=H, R^2=Me) rearranged to 2-methylimidazo [1,2-*c*]pyrimidine (**10;** R^1=Me, R^2=R^3=H) about 130 times faster than 3–methylimidazo[1,2-*a*]pyrimidine. The few rearrangements attempted with acidic media were unsuccessful. Thus, 3-methylimidazo[1,2-*a*]pyridine in 10% aqueous HCl and 3,7-dimethyl-5-oxo-8*H*-imidazo[1,2-*a*]pyrimidine in formic acid were unchanged after 24 h at 90°C. In the case of imidazo[1,2-*a*]- or [1,2-*c*]pyrimidines, the mechanism is further complicated by the possibilities of 1,4-addition and tautomerism. The kinetic results are best explained by an initial rate-determining attack at position 5 by hydroxide ion. The driving force for this first step is electronic in nature, since it is dependent on the electrophilicity of position 5. On the other hand, the formation of hydrated intermediate **8a** should relieve the steric interaction between groups R and R^1 (71JHC643) as a consequence of the change in hybridiza-



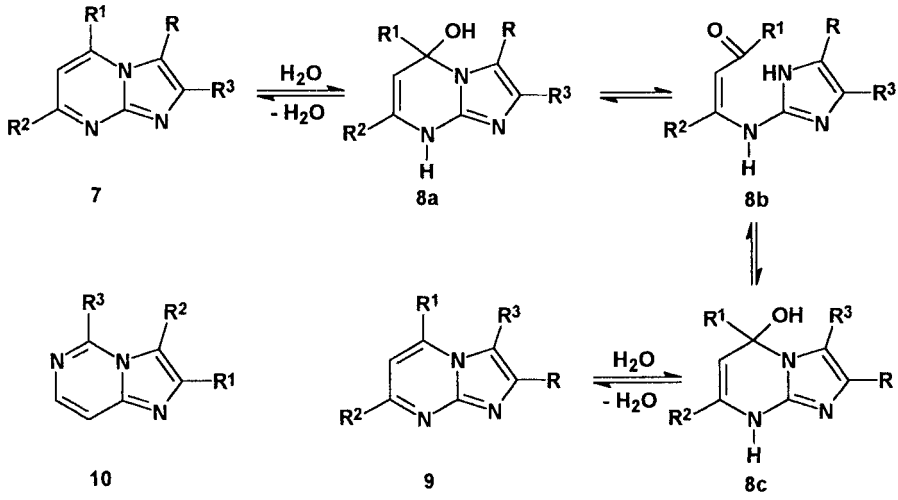
1 R^1 = R^5 = H, R^4 = NO_2
2 R^1 = R^4 = H, R^5 = NO_2
3 R^3 = R^4 = R^5 = H, R^2 = $CH_2\overset{+}{P}Ph_3\bar{B}r$

4 R^1 = R^5 = H, R^4 = NO_2
5 R^1 = R^4 = H, R^5 = NO_2
6 R^3 = R^4 = R^5 = H, R^2 = $CH_2\overset{+}{P}Ph_3\bar{B}r$

SCHEME 2

tion of carbon-5 upon hydration; this stabilizes **8a** and **8c** compared to **7** and **9,** respectively. Following hydration, the six-membered ring undergoes tautomeric ring opening to intermediate **8b,** which cyclizes and dehydrates to give **9.** The fission of the 4–5 bond is more likely to occur in **8a** rather than in **8c** because of the residual interaction between the 3 and 5 substituents. This is in agreement with the increase in rate found on passing from 3-methyl- to 3,5-dimethyl imidazo[1,2-*a*]pyrimidines and from 3,7-dimethyl- to 3,5,7-trimethylimidazo [1,2-*a*]pyrimidines. Moreover, the larger the interaction between the groups, the more the equilibrium is shifted toward **9.** 2-Methylimidazo[1,2-*a*]pyrimidine (**9;** R=Me, R^1=R^2=R^3=H) and 2,7-dimethylimidazo[1,2-*a*]pyrimidine (**9;** R=R^2=Me, R^1=R^3=H) are thus predicted to be more stable than the isomeric 3-methylimidazo [1,2-*a*]pyrimidine and 3,7-dimethylimidazo[1,2-*a*]pyrimidine, respectively (71JHC 643).

Methyl substituents are known to slow down the rate of ring opening. Thus, a retarding effect of a 7-methyl substituent in the rearrangement of the imidazo[1,2-*a*]pyrimidine system was found (71JHC643). The existence of a peri-interaction between two substituents, at positions 1 and 8 or at 3 and 5, has been established in polyazaindolizine systems. The rearrangement was also observed in imidazopyrimidylmethyl phosophonium salt **7** (R^1=R^2=H, R=$CH_2P^+Ph_3Br^-$) and **10** (R^2=$CH_2P^+Ph_3Br^-$, R^3=OH) to give the Dimroth products **9** (R^1=R^2=H, R=$CH_2P^+Ph_3Br^-$) and **10** (R^1=CH_2P^+ Ph_3Br^-, R^3=OH), respectively (75LA1934) (Scheme 3).



SCHEME 3

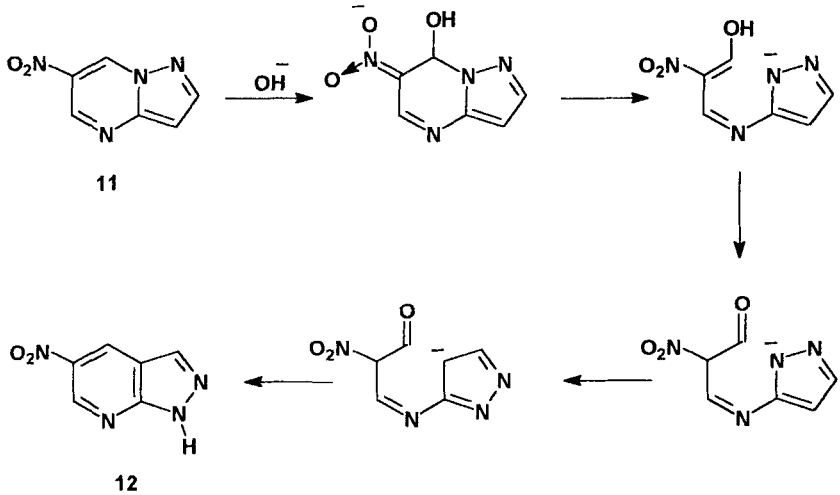
B. Rearrangement of Pyrazolo Heterocycles

The pyrazolo[1,5-*a*]pyrimidine **11** underwent a pyrimidine ring opening and then recyclization when heated with aqueous alcoholic alkali to give pyrazolo[3,4-*b*]pyridine **12.** Similarly, 2-hydroxy-5,7-dimethylpyrazolo [1,5-*a*]pyrimidine rearranged to 3-hydroxy-4,6-dimethyl[3,4-*b*]pyridine (94MI1). The presence of the nitro group in **11** is necessary in the open-chain monocyclic intermediate in order to proceed to the pyrazolopyridine ring, which otherwise recyclizes back to the starting compound **11** due to the more nucleophilic character of the C4 of the pyrazole ring than the nitrogen atom at position 1 (Scheme 4).

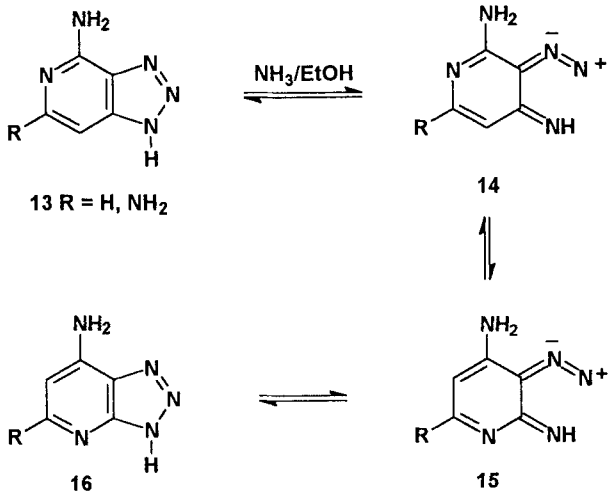
C. Rearrangement of 1,2,3-Triazolo Heterocycles

1. *1,2,3-Triazolopyridines*

The Dimroth rearrangement of mono- and diamino-1*H*-1,2,3-triazolo [4,5-*c*]pyridines **13** to mono- and diamino-3*H*-1,2,3-triazolo[4,5-*b*]pyridines **16** took place in ethanolic ammonia and involves diazo-type intermediates **14** and **15** (72JOC3601; 73JOC1095). The thermodynamic stability of **16** is greater than that of **13** in the presence of ammonia since treatment of **16** with ethanolic ammonia gave no rearrangement (Scheme 5).



Scheme 4

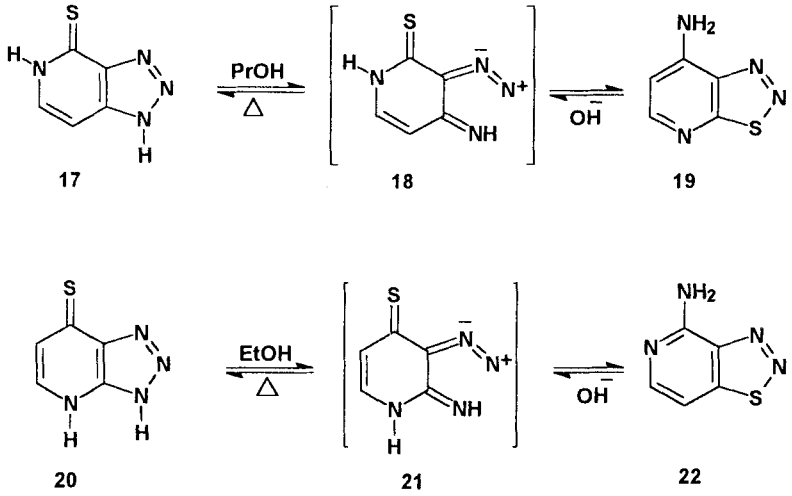


SCHEME 5

The rearrangement of 1,2,3-triazolopyridinethione **17** to amino-1,2,3-thiadiazolopyridine **19** suggested that opening of the triazole ring to intermediate **18** is controlled by the electron-withdrawing effect of the substituent on the pyridine ring (HNCS or NCSH > $NCNH_2$). Opening of the thiadiazole ring of **19** with base gave the electron-donating anion of the pyridinethione intermediate, which favored triazole ring formation (72JOC3601). On the other hand, when **20** was heated in ethanol, it rearranged to **22** presumably *via* **21.** Treatment of **22** with aqueous NaOH in ethanol reversed the rearrangement to give **20** (72JOC3601) (Scheme 6).

2. *1,2,3-Triazolopyrimidines*

Heating a solution of triazolopyrimidine **23** in dimethylacetamide (DMAC) gave mainly the rearranged product **24** and traces of unchanged **23** while under the same condition **24** gave the unchanged **24** and a trace of the rearrangement product **23** [72JCS(CC)52]. The rearrangement into **24** depends on the temperature and basicity of the solvent because different percentages of **24** were obtained. In boiling pyridine the isomer mixture was not at equilibrium and gave **24** and traces of **23.** The rearrangement in pyridine proved to be irreversible; heating **24** at reflux in this solvent for the same period of time did not give **23.** Presumably this rearrangement involves a 5-diazo pyrimidine intermediate which favors ring closure to the amino group of greater nucleophilicity. However, attempted trapping of



17 18 19

20 21 22

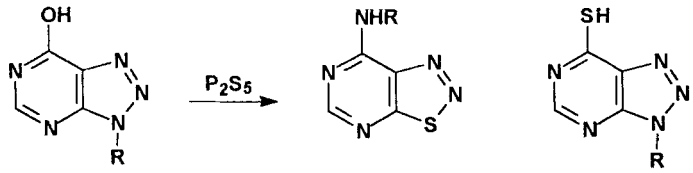
SCHEME 6

this intermediate was unsuccessful. When a solution of **23** in dibutylamine was heated, no rearrangement to **24** was observed and this suggested that the anion of **23** underwent rearrangement less readily than **23** itself, i.e., the amount of rearrangement decreased as the concentration of the anion of **23** increased. Although, this result suggested that the rearrangement of **24** to **23** might be favored by a strong base and anion formation, no rearrangement was observed when a solution of **24** was heated in dibutylamine (Scheme 7).

When 7-hydroxy-1,2,3-triazolo[4,5-*d*]pyrimidine (**25**) and its 3-benzyl derivative were thiated by phosphorus pentasulfide, they gave 7-amino (and benzylamino)thiazolopyrimidine (**26**), respectively, instead of the expected 7-mercapto isomer **27** [67JCS(C)1856]. The thermal rearrangement of the benzylated isomer reaches an equilibrium point which favors the thiazolo isomer. The rates for such equilibration in a series of analogs of 7-mercapto-

23 24

SCHEME 7



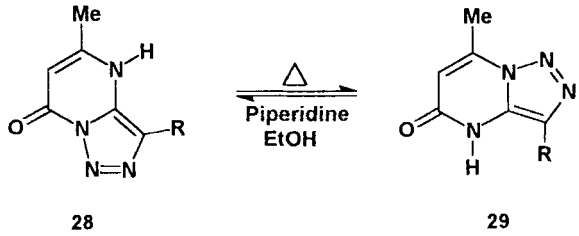
SCHEME 8

3-phenyltriazolopyrimidine **27** and 7-anilinothiazolopyrimidine **26,** having a variety of *para* substituents, decrease as the electron-withdrawing power of the aryl group increases due to the effect of the aryl group on the rupture and/or formation of the 2–3 bond in **27** or its isomer **26.** The aryl group is so far from this bond in **26** that the energy of interaction between the two is probably minimal and unaffected by the change in R. In contrast, the aryl group must strongly affect the polarization of the 2–3 bond in isomer **27,** and increasing electron withdrawal by R should favor isomer **26** at equilibrium (Scheme 8).

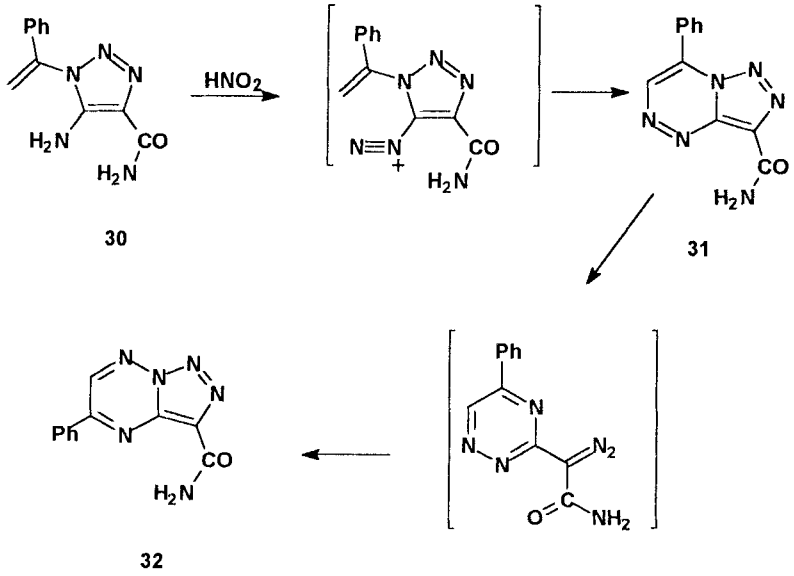
A reversible Dimroth rearrangement was found on heating 1,2,3-triazolopyrimidine **28;** isomer **29** was obtained. Reformation of **28** from the latter by heating with piperidine in ethanol was also observed [73JCS(P1)943] (Scheme 9).

3. *1,2,3-Triazolotriazines*

The diazotization of 5-amino-4-carbamoyl-1-(α-styryl)-1,2,3-triazole (**30**) gave 5-phenyl-1,2,3-triazolo[1,5-*b*][1,2,4]triazine-3-carboxamide (**32**) as a result of rearrangement of the initially formed 7-phenyl-1,2,3-triazolo[5,1-*c*][1,2,4]triazine-3-carboxamide (**31**). Compound **32** is favored thermodynamically and its structure was confirmed by an X-ray crystallographic study (88BSB179) (Scheme 10).



SCHEME 9



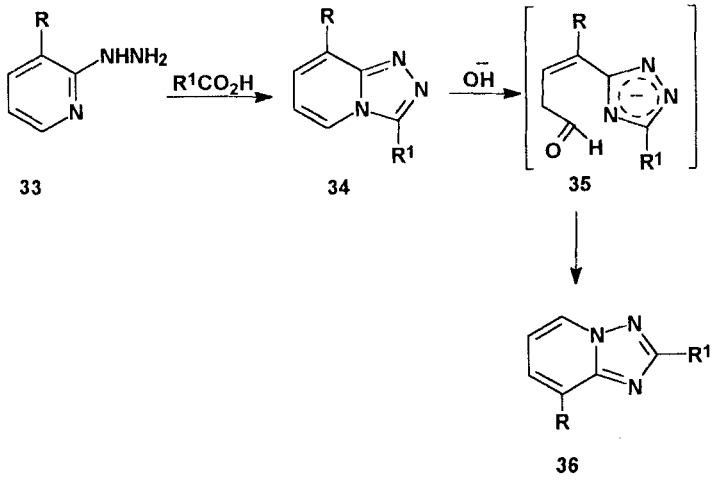
SCHEME 10

D. REARRANGEMENT OF 1,2,4-TRIAZOLO HETEROCYCLES

Various fused heterocyles which have five-membered rings of the 1,2,4-triazole type are reported to rearrange. This type is important because of the facility of the rearrangement, to an extent that the expected initial products of cyclization often cannot be isolated.

1. *1,2,4-Triazolopyridines*

2-Hydrazinopyridine derivatives **33** undergo cyclization to 1,2,4-triazolo-[4,3-*a*]pyridines **34** when boiled in formic or other carboxylic acids. Compounds **34** rearranged in a basic medium to give the 1,2,4-triazolo[1,5-*a*]-pyridines **36.** Such rearrangement was facilitated by the presence of electron-attracting groups such as the nitro group on the 3-position of the pyridine ring (66JOC265; 90JHC1649). The rearrangement most likely involves an initial hydroxide ion attack at the C-5 position to yield intermediate **35,** which then undergoes ring closure at N-1, a more basic site than N-4 in the 1,2,4-triazole anion. The stability of this anion is the controlling factor in the rearrangement (66JOC265) (Scheme 11).



33 34 35 36

SCHEME 11

2. *1,2,4-Triazolopyrimidines*

Isomerization of various types of 1,2,4-triazolopyrimidines occurs smoothly; heat alone is sufficient. This extreme ease can be attributed to the increase in the electron deficiency at the C-5 center owing to the second nitrogen atom of the pyrimidine ring.

a. *1,2,4-Triazolo[4,3-a]pyrimidines.* Treatment of 2-hydrazinopyrimidine **37** with *ortho* esters gave the 1,2,4-triazolo[4,3-*a*]pyrimidine **38,** which has alkyl or aryl groups at the 3-,5-,6-, or 7-positions. They can rearrange under acidic conditions to give the corresponding 1,2,4-triazolo-[1,5-*a*]pyrimidine **39,** which can be also prepared by the reaction of 2-hydrazinopyrimidine **37** with formic acid (71CB2702; 76KGS706; 77AJC2515).

Classic Dimroth rearrangements have usually occurred in neutral molecules under alkaline conditions (94MI1), although some weakly basic substrates have undergone rearrangement only under acidic conditions (69ZC241). The system **38** underwent rearrangement in both alkaline and acidic media but not under neutral conditions.

Substitution on the parent heterocycle **38** by alkyl groups affected the rate of rearrangement and in the same direction, whether in acidic or alkaline media. The presence of a 3-methyl or 3-ethyl substituent on **38** decreased the rate of rearrangement as a result of electron donation by the substituent to the electron-deficient system (63JCS1276). In contrast, electron-withdrawing substituents increased the rate of rearrangement. The

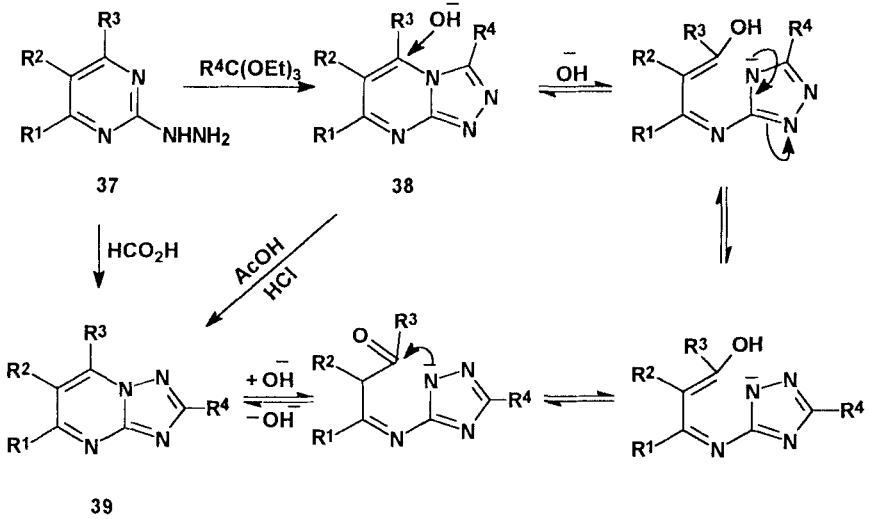
6-methyl and 7-methyl derivatives rearranged six times slower than the parent compound. The 5 isomer rearranged much more slowly, due to steric hinderance of the 5-methyl group toward the attack at the 4–5 bond prior to fission. For the same reason, the 3,5- and 5,7-dialkyl derivatives rearranged extremely slowly. The slowest rearrangement occurred in the 3,5,7-trialkyl derivatives. The rates for rearrangement in acidic media followed the order of those in alkali (77AJC2515) (Scheme 12).

A mixture of triazoles **41** and **42** was formed on heating hydrazine **40** in formic acid (76KGS706).

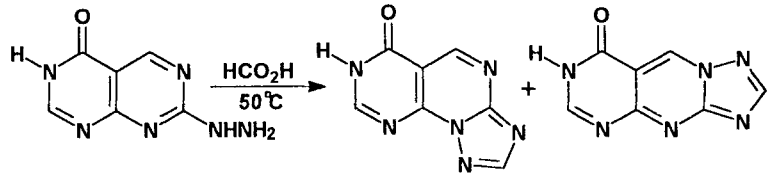
Bis-1,2,4-triazolo[4,3-*a*:4′,3′-*c*]pyrimidine **43** and *bis*-1,2,4-triazolo [4,3-*a*:1′,5′-*c*]pyrimidine **45** are stable toward rearrangement in acid or alkali but system **43** did undergo a thermal Dimroth-like rearrangement into *bis*-1,2,4-triazolo[1,5-*a*:4′,3′-*c*]pyrimidine **44** on fusion above 300°C (79AJC1585).

The reaction of triazoles **46** and **51** with NaOH gave **47** and **48,** respectively. The later triazoles were formed by the reaction of **49** with NaOH or NaOH in H_2O_2, respectively. When the [1,5-*a*]triazole **49** was treated with H_2SO_4, it afforded surprisingly the [4,3-*a*] isomer **50** and not the amide **47** because a retro-Dimroth rearrangement happened (70JPR254) (Schemes 13, 14, and 15).

When [4,3-*a*]triazoles **A** were heated in a dilute solution of KOH in ethanol or fused above their melting points, they gave [1,5-*a*]isomers **C.** Treatment of 2-benzalhydrazino-5-cyano-6-phenyl-3,4-dihydropyrimidin-4-

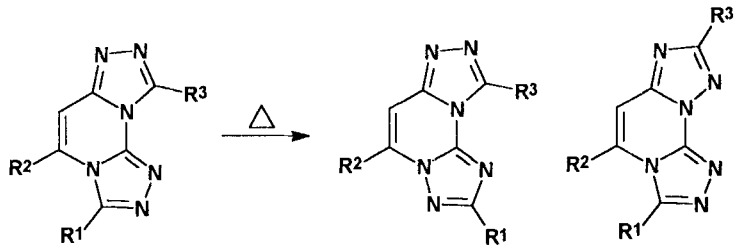


SCHEME 12



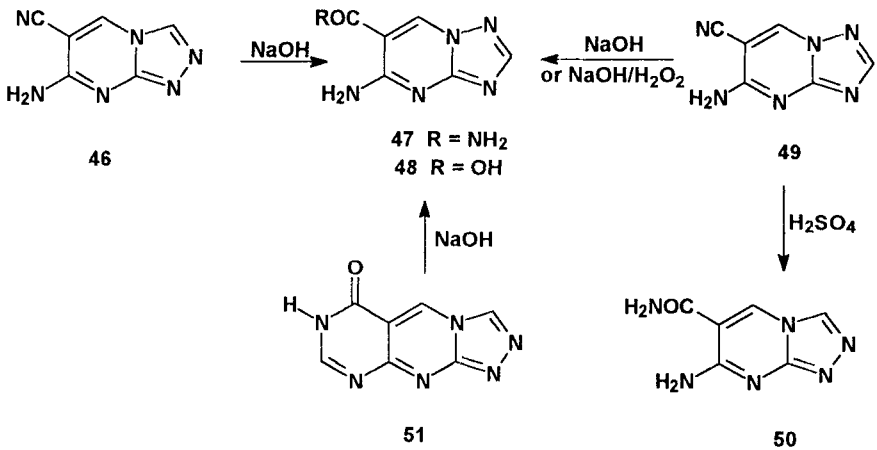
40 41 42

SCHEME 13



43 44 45

SCHEME 14



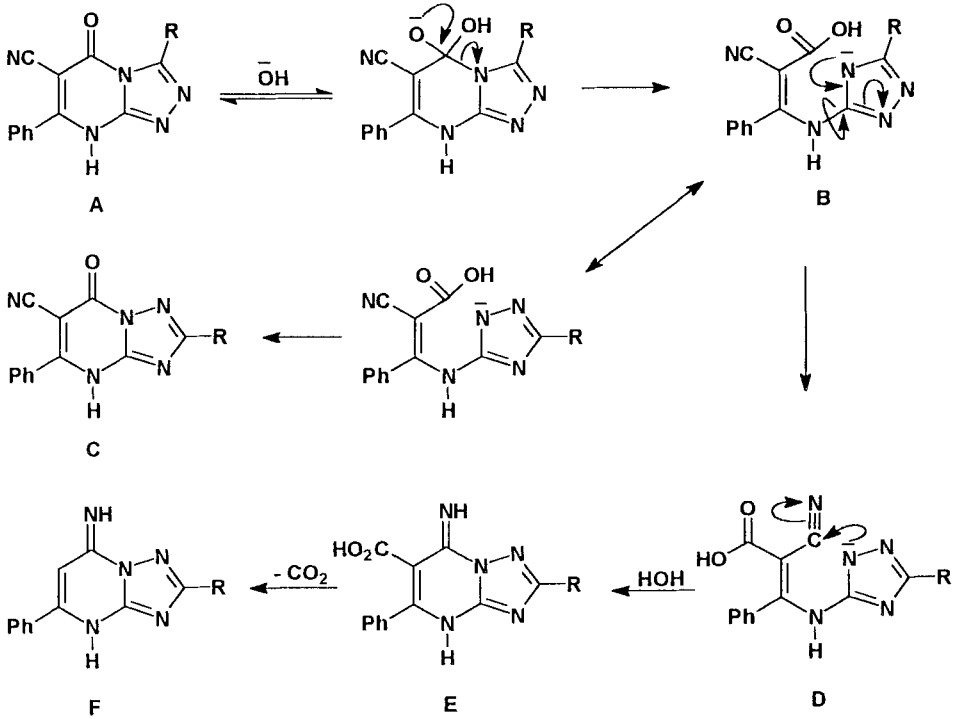
46 47 R = NH2 48 R = OH 49 50 51

SCHEME 15

one with bromine in acetic acid gave 6-cyano-2,5-diphenyl-7-oxo-1,2,4-triazolo[1,5-*a*]pyrimidine (**C,** R=Ph) (98ZN1203). The use of more concentrated alkali in the Dimroth rearrangement of **A** led to the participation of the nitrile group in the cyclization step after the formation of the ring-opened intermediate **B** that isomerized to **D** which then cyclized to **E.** Decarboxylation of **E** gave **F** (Scheme 15a) (98ZN1203).

b. *1,2,4-Triazolo[4,3-c]pyrimidines.* The above considerations have been shown to apply in the rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidine-3-thiol to 1,2,4-triazolo[1,5-*a*]pyrimidine-2-thiol under acidic, basic, or thermal conditions. On the other hand, 1,2,4-triazolo[4,3-*a*]pyridine-3-thiol was stable under acidic or thermal conditions and with base it underwent decomposition to 2-pyridone (63JCS56412; 65JCS3357).

The condensation of 4-hydraziopyrimidie **52** with *ortho* esters led to the formation of 1,2,4-triazolo[4,3-*c*]- and [1,5-*c*]pyrimidines, where the reaction was found to be dependent on the structure of the *ortho* ester (78AJC2505; 86TL3127; 89JHC687). Thus, the *ortho* acetate gave the unre-



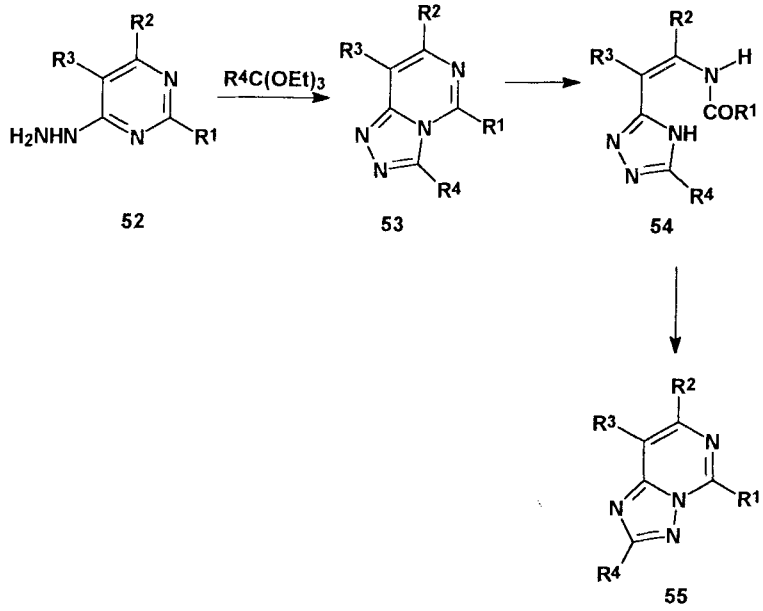
SCHEME 15A

arranged products, i.e., the [4,3-*c*] isomer, which upon heating at a higher temperature gave the [1,5-*c*] isomer (58CB1395; 59CB903). On the other hand, when the reaction was performed by using ethyl *ortho* formate, the rearranged product was directly formed in the case of the 5-methoxy derivative **52,** while both isomers were obtained from the corresponding benzyloxy derivative **52.**

The 1,2,4-triazolo[4,3-*c*]pyrimidine **53** underwent rearrangement in glacial acetic acid to the [1,5-*c*] isomer **55,** *via* the acylaminoalkenyltriazole intermediate **54** (78AJC2505); compounds **53–55** are distinguished by their UV spectra. In aqueous buffers, these reactions stop at triazole **54** except in the presence of a 7-methyl group, which helps completion of the sequence. The ring fission of **53** to **54** is retarded by 5- and/or 8-methyl groups but accelerated slightly by 3- and/or 7-alkyl groups. The triazolo[1,5-*c*]pyrimidine **55** underwent a slow ring fission to triazole **54,** which was retarded by the presence of 2-, 5-, or 8-alkyl groups and totally stopped by a 7-methyl group.

In contrast with the smooth rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidines into their [1,5-*a*] isomers, rearrangement from the [4,3-*c*] to the [1,5-*c*] system **53** to **55** was complicated by the relative stability of intermediate **54** (77AJC2515). It emerged that both reactions were acid–base catalyzed, although the triazolo[4,3-*c*]pyrimidine **53** underwent hydrolytic fission 175 times faster than its [4,3-*a*] isomer at pH 3 and 5 times faster at pH 11. The 1,2,4-triazolo[4,3-*a*]pyrimidine underwent complete rearrangement in aqueous buffers, whereas its [4,5-*c*] isomer did not. This was explained by a consideration of the nature of their respective ring fission products; one has a reactive hydroxymethylene group ready for recyclization, whereas the other has a relatively unreactive amide. In contrast to its behavior in aqueous buffer, the triazolo[4,3-*c*]pyrimidine **53** rearranged completely into its [1,5-*c*] isomer **55** in glacial acetic acid (Scheme 16).

Dimroth rearrangement of 5-benzyl-7-methyl-1,2,4-triazolo[4,3-*c*]pyrimidine (**56**) to 7-benzyl-5-methyl-1,2,4-triazolo[1,5-*c*]pyrimidine (**57**) was effected in boiling ethanolic sodium ethoxide or in an alcoholic solution of triethylamine. In case of ethanolic potassium hydroxide containing a small amount of water, the conversion took place after 3–5 min in cold conditions, but further boiling led to destruction of the molecule (92KGS225). The PMR spectra of compounds **56** and **57** differ in the downfield region. The signal at 4.40 ppm, corresponding to the CH_2 fragment of the benzyl group, first disappeared with a change in the signals for the protons of the phenyl group (conversion of the singlet of the aromatic protons into a multiplet). This change was due to the electronic effect of the nitrogen atom at position 1, which led to some restricted rotation of the phenyl group. The signal of the pyrimidine proton in the spectrum of **57** was shifted downfield (8.08 ppm), whereas it was superimposed with those of the aromatic protons in a singlet at 7.23 ppm. The initial disappearance of the signal for the

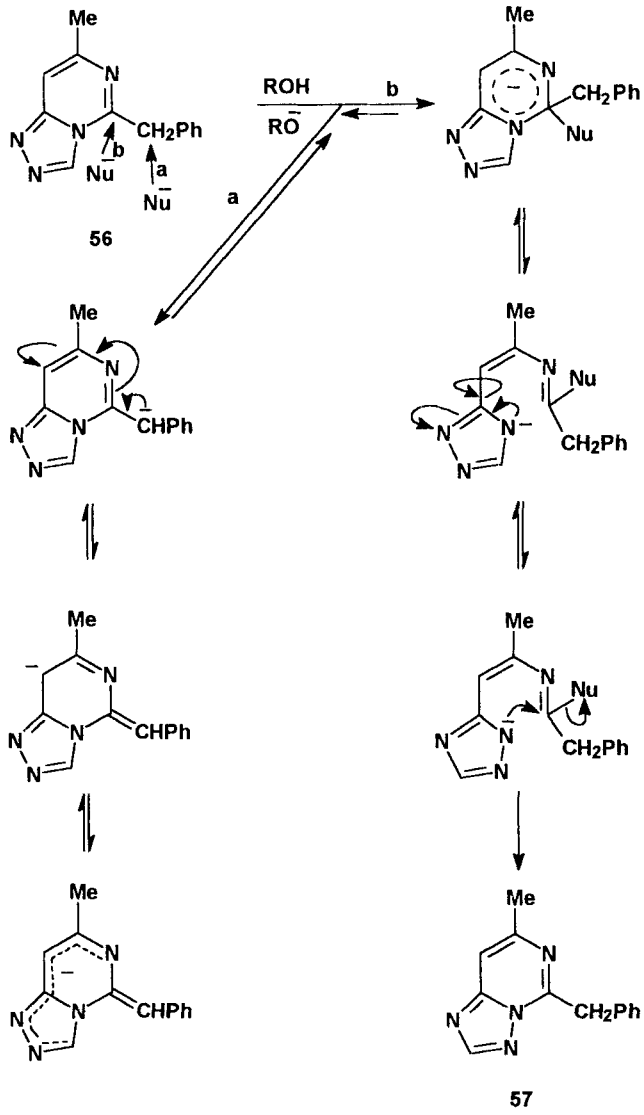


SCHEME 16

protons of the methylene group was due to their high CH acidity, which leads to isotopic exchange in base. Thus, initial attack by the nucleophilic takes place in two alternative ways: the reversible removal of a proton from the benzyl group (a) and/or nucleophilic attack by the alkoxy group at position 5 (b). The seconed possibility led to ring opening and recyclization at another nitrogen atom of the triazole ring (92KGS225). Hence, while the first route did not promote the rearrangement, it did not prevent the second as a consequence of its reversibility.

The 8-allyl derivative of **56** can be rearranged to the respective propenyl derivative of **57** by the action of sodium ethoxide (93KGS1545) (Scheme 17).

The cyclization of 4-hydrazinothieno[2,3-*d*]pyrimidine **58** with triethyl *ortho* formate gave the 1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine **59,** whereas its cyclization with formic acid gave the isomeric 1,2,4-triazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine **60** (81JHC43). It was reported later (85JHC831) that the triazolothienopyrimidines formed by the cyclization of 4-hydrazino-2-phenylthieno [2,3-*d*]pyrimidine with triethyl *ortho* formate or formic acid have the 1,2,4-triazolo[4,3-*c*]thieno[3,2-*e*]pyrimidine structure because of their failure to isomerize under acid catalysis, but under basic conditions isomerization yielded the 5-phenyl-1,2,4-triazolo[1,5-*c*]-thieno[3,2-*e*]pyrimidine (85JHC831). Proton magnetic resonance spectroscopy showed that the triazole proton of triazolo[4,3-*c*] isomers are more



SCHEME 17

deshielded than that of [1,5-*c*] isomers (81JHC43). Thus, e.g., triazoles **59** exhibit the triazole proton signal about 8.4 ppm.

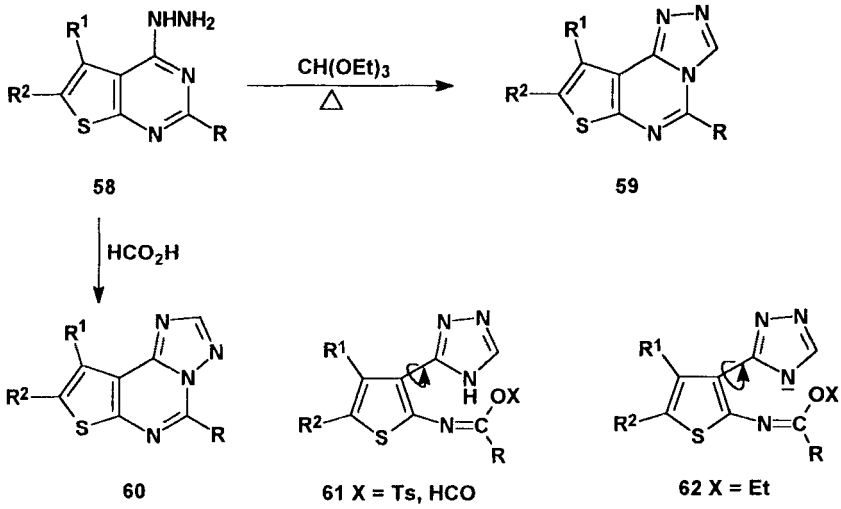
The isomerization proceeds by the formation of ring-opened intermediates **61** or **62** in the presence of acids, such as *p*-toluenesulfonic or formic acids, or bases like sodium ethoxide.

5-Unsubstituted, 5-alkyl, and 5-aralkyltriazolo [4,3-*c*]thienopyrimidines undergo isomerization to [1,5-*c*] isomers under acidic and basic conditions, whereas 5-phenyl and 5-styryl-1,2,4-triazolo[4,3-*c*] thienopyrimidine resist the isomerization under acidic conditions. This inability to isomerize under acidic conditions could be due to the stabilization through delocalization of the charge on the pyrimidine system **63** and **64** (85JHC831) (Schemes 18 and 19).

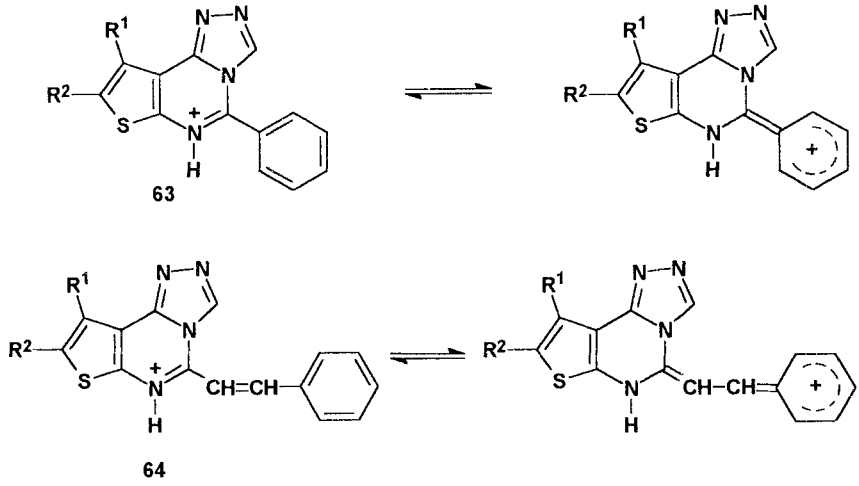
When 5-methylthio-7-amino-1,2,4-triazolo[1,5-*c*]pyrimidine **65** was heated in hydrazine hydrate, 5-hydrazino-7-amino-1,2,4-triazolo[1,5-*c*]pyrimidine **66** was obtained and **66** underwent rearrangement to give isomer **67** (79KGS262). This a rare example of the retro-Dimroth rearrangement (Scheme 20).

3. *1,2,4-Triazoloquinazolines*

The reaction of 4-hydrazinoquinazoline **68** with *ortho* esters in the presence of K_2CO_3 gave 1,2,4-triazolo[4,3-*c*]quinazoline **69,** while aliphatic acids always yielded the 1,2,4-triazolo[1,5-*c*]quinazoline **70** by rearrangement of the [4,3-*c*] system **69.** Omission of K_2CO_3 resulted in a mixture of the two isomers (70JOC3448). Acylation of **68** with EtO_2CCOCl followed by cyclization with AcOH gave **70** (83GEP3204126). The high-field chemical shifts of the 2-substituents in 2-substituted 1,2,4-triazolo[1,5-*c*]quinazo-



SCHEME 18

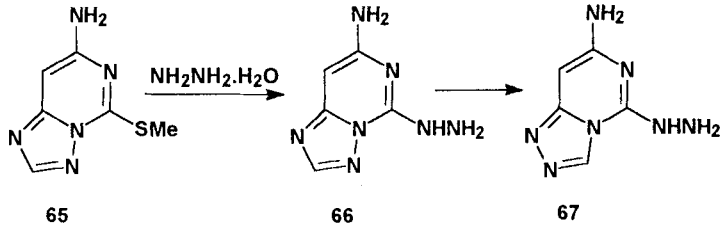


SCHEME 19

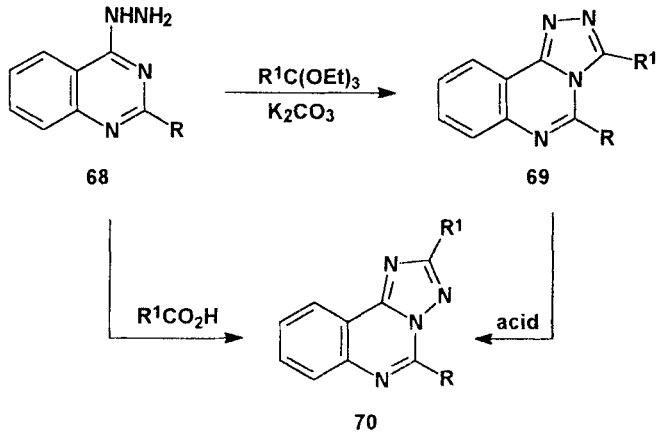
line compared to those of the corresponding 3-substituents in 3-substituted 1,2,4-triazolo[4,3-*c*]quinazolines serve to differentiate between the two isomers. The above isomerization involved covalent hydration of the 5–6 double bond of **69** followed by ring opening and subsequent ring closure at N1 of the triazolo nucleus. The isomerization also can occur with extreme ease in the presence of alkali (Scheme 21).

4. *1,2,4-Triazolopyrazines*

The 1,2,4-triazolo[4,3-*a*]pyrazine system underwent rearrangement to the isomeric 1,2,4-triazolo[1,5-*a*]pyrazine system, although in poor yield (66JOC265).



SCHEME 20



SCHEME 21

5. *1,2,4-Triazoloquinoxalines*

The 1,2,4-triazolo[4,3-*a*]quinoxaline system failed to undergo rearrangements (66JOC265) similar to those found with 1,2,4-triazolopyridines, -pyrazines, and -pyrimidines.

6. *1,2,4-Triazolothiazines*

Heating 2-hydrazono-3,4-dihydro-2*H*-1,3-benzothiazin-4-one (**71**) with *ortho* esters in xylene gave 1,2,4-triazolo[3,4-*b*][1,3]benzothiazin-5-one (**72**) (90JHC391). However, when **71** was treated with trifluoroacetic anhydride or trichloroacetic anhydride in DMF at 4°C it gave only the open-chain intermediates **73.** Subsequent heating in DMF or DMSO of the trifluoroacetyl derivative of **73** afforded the unexpected rearranged ring-closure product 2-trifluoromethyl-1,2,4-triazolo[5,1-*b*][1,3]benzothiazin-9-one (**74**) *via* Dimroth rearrangement. No reaction was observed with the trichloroacetyl derivative due to its bulk, which hindered the cyclization. This observation also was made when trichloroacetyl chloride was used instead of the respective *ortho* ester.

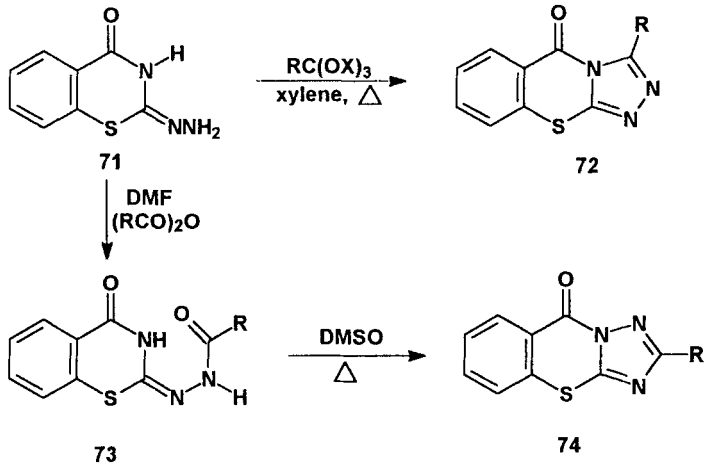
Treatment of **71** with chlorocarboxylic acid chlorides in DMF at 4°C afforded the cyclized unrearranged products **72** in low yields and the corresponding open-chain intermediates **73** in high yields; no rearranged products were isolated. However, when the above reactions were performed at 35°C, the rearranged products **74** were produced along with a major amount of **72.** In the case of chloroacetyl chloride at 35°C, the expected unrearranged product **72** was the only product.

The reaction of **71** and ethoxyoxalyl chloride at 4°C in DMF gave only the open-chain product **73** (R=CO_2Et), while on heating at 35°C the disubstituted compound **75** with a small amount of the rearranged product **76** were produced (90JHC391).

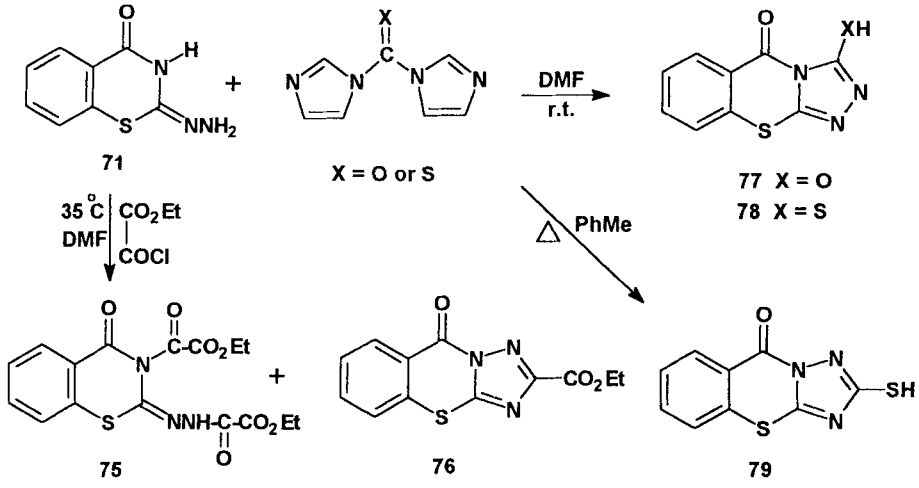
The reaction of **71** with *N,N'*-carbonyldiimidazole or its thio analog in DMF at room temperature afforded only the unrearranged product 3-hydroxy-1,2,4-triazolo[3,4-*b*][1,3]benzothiazin-5-one (**77**) or its thio analog **78,** respectively. However, heating **71** with *N,N'*-thiocarbonyldiimidazole in toluene gave the cyclized rearranged product mercaptotriazolobenzothiazine **79** (90MI1) (Schemes 22 and 23).

7. *1,2,4-Triazolo-1,2,4-triazines*

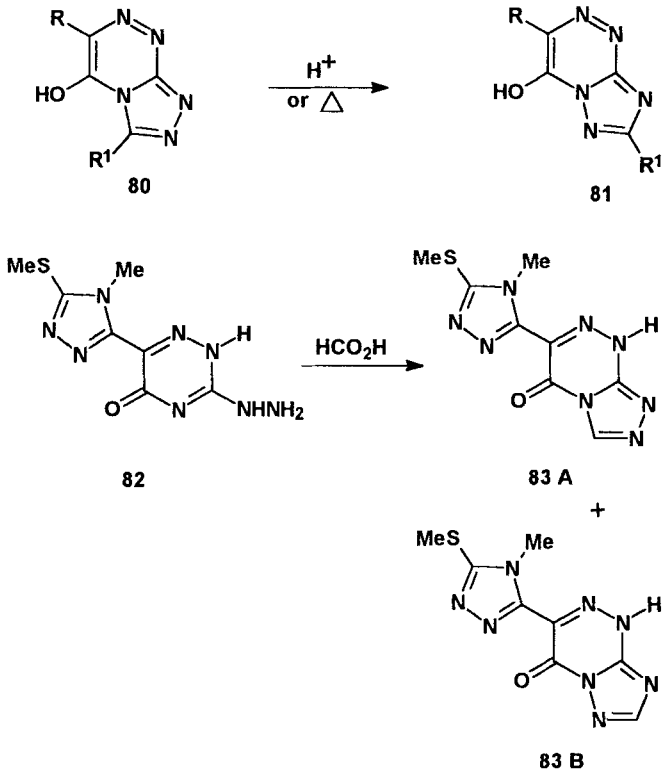
The triazolo[3,4-*c*][1,2,4]triazine **80** underwent Dimroth rearrangement on heating or on treatment with acid to give triazolo[5,1-*c*][1,2,4]triazine **81** [75BSF857]. However, the reaction of hydrazine **82** with formic acid gave a mixture of triazolo[3,4-*c*][1,2,4]triazine **83A** and triazolo[5,1-*c*][1,2,4]triazine **83B** [75BSF864]. Similarly, the reaction of 5-alkyl-3-carboxyhydrazino-1,2,4-triazole with triethyl *ortho* formate gave 2-substituted 1,2,4-triazolo[1,5-*d*] and 3-substituted 1,2,4-triazolo[4,3-*d*][1,2,4]-triazin-8-one (81T4353) (Scheme 24).



SCHEME 22



SCHEME 23

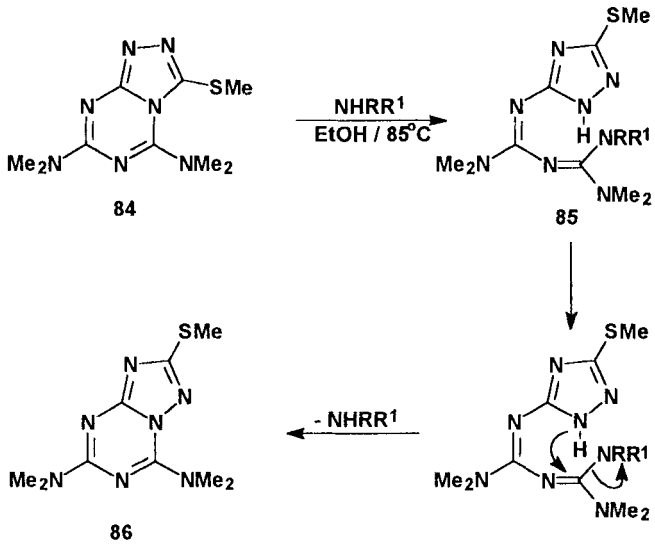


SCHEME 24

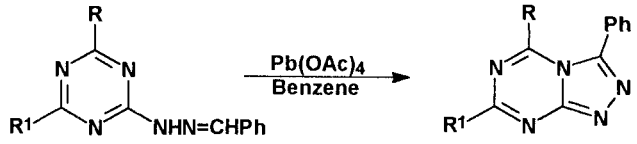
8. *1,2,4-Triazolo-1,3,5-triazines*

5,7-*Bis*(dimethylamino)-3-(methylthio)-1,2,4-triazolo[4,3-*a*][1,3,5]triazine (**84**) has been isomerized to its [1,5-*a*] isomer **86** upon being treated with excess anhydrous dimethylamine, pyrrolidine, or aniline in absolute ethanol at 85°C. This rearrangement generally occurs through attack on the six-membered ring by the basic ion to give the guanidine intermediate **85,** which upon ring closure gave the final product. The rearrangement of **84** can occur also in an acidic medium but a mixture of the two isomers was formed (73JHC231) (Scheme 25).

When the hydrazone **87** was treated with lead tetraacetate in benzene at 20–30°C, it afforded the corresponding 1,2,4-triazolo[4,3-*a*][1,3,5]triazine **88,** whereas the [1,5-*a*] isomer was not formed (70T3357). On the other hand, when the hydrazines **89** (R=Me, R^1=H or Me) were allowed to react with methyl diethoxyacetate for a short time and at a moderate temperature, the corresponding bicyclic products of the [4,3-*a*] series **90** [R=Me, R^1=H or Me] were obtained. However, when **89** [R=R^1=H] was heated with an excess of this reagent under reflux for 10 min the isomeric product [1,5-*a*] system **91** was formed (70T3357) (Schemes 26 and 27).



SCHEME 25



87 88

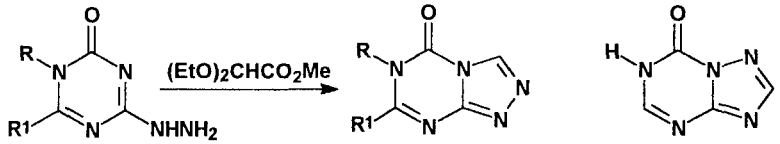
SCHEME 26

E. REARRANGEMENT OF PYRIMIDO HETEROCYCLES

When 3-β-**D**-ribofuranosyl-9*H*-9-oxo-7-methoxycarbonylpyrimido[2,1-*i*]-purine **a** was acetylated, it gave the corresponding tri-*O*-acetyl derivative accompanied by 40% conversion to the other isomer, 3-[2′,3′,5′,-tri-*O*-acetyl-(β-**D**-ribofuranosyl)]-7*H*-7-oxo-9-methoxycarbonylpyrimido[2,1-*i*]-purine **b,** *via* probably Dimroth rearrangement due to ring opening of **a** by the nucleophilic attack of either pyridine or the acetate ion, followed by ring closure facilitated by the leaving group properties of the acetate ion. Similarly, treatment of **a** or **d** with dimethylamine gave the same imidazolylpyrimidinone derivative **c,** which could be recyclized under acidic conditions to the thermodynamically favored fluorescent 7-oxopyrimido-[2, 1-*i*]purine isomer **d** (Scheme 27a) (95H1197).

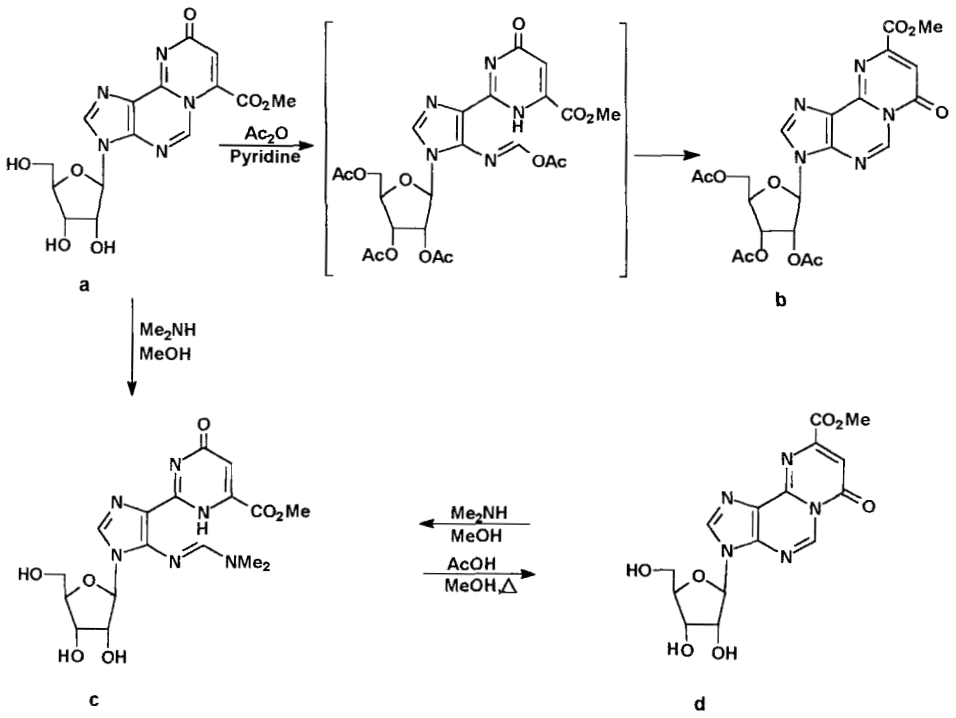
III. Translocation of Exo- and Endocyclic Heteroatoms in Heterocyclic Rings

This type of rearrangement represents one of the first examples leading to the generalization of a Dimroth rearrangement. The exo- and endocyclic heteroatoms may exist as a part of acyclic systems. However, this section



89 90 91

SCHEME 27



SCHEME 27A

deals only with those that have one of the heteroatoms in a heterocyclic system.

A. HETEROCYCLES WITH ONE HETEROATOM IN THE RING

1. *Pyridines*

Although 1,2-dihydro-2-imino-1-methylpyridine (**92,** R=H) was hydrolyzed slowly in alkali to the oxo analog **93** without rearrangement (21CB814), the corresponding derivative (**92,** $R=NO_2$), with a powerful electron-withdrawing group, rearranged to 2-methylamino-5-nitropyridine (**94**) (28CB1223). 1-Diphenylmethyl-1,2-dihydro-2-iminopyridine was rearranged under only extreme conditions (25CB393; 52DOK223). Rearrangement of 1-alkyl-2-(alkylimino)-6-amino-4-(alkylamino)-1,2-dihydro-3-pyridine carbonitrile by the action of amine gave 2,4,6-*tris*(alkylamino)-3-pyridine carbonitrile (81CB937).

Interestingly, the isotopically labeled 2-aminopyridine **95** was partly isomerized into the isomer **96** after heating in aqueous acid or ammonia (66ZC181) (Schemes 28 and 29).

The acid treatment of 1-aminopyridine derivatives possessing strong electron-withdrawing groups at C4 as in **97** gave pyrazolopyridines **98;** Dimroth rearrangement had taken place followed by cyclization (84PJC85) (Scheme 30).

When 1-dicyanomethylene-3-indanone was treated with trimethyl *ortho* formate and a substituted aniline in the presence of AcOH it gave anilinomethylene-indanone **99** followed by ring closure and Dimroth rearrangement to indanopyridine **100** (89M781) (Scheme 31).

2. *Azepine*

Rearrangement of the 6,11-dioxo-5,6-dihydromorphanthridines by heating in trifluoromethanesulfonic acid gave 1-aminoanthraquinone [95JAP-(K)07/149698] (Scheme 31A).

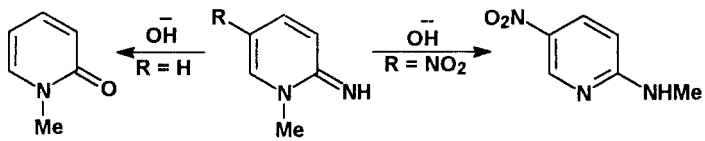
3. *Thiopyrans*

4-Amino-2-alkylaminothiopyranylium iodide **101** was rearranged by heating in DMF in the presence of NaOEt to 1-alkyl-4-aminodihydro-2(1*H*)-pyridinethione **102** (83M581). Similarly, naphthothiopyran **103** underwent the rearrangement with NaOH to give **104** (86CS639) (Schemes 32 and 33).

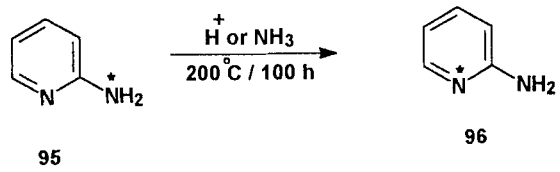
B. Heterocycles with Two Heteroatoms in the Ring

1. *Imidazoles*

2-Amino-1-methyl-1*H*-imidazole-4,5-dione (**105**) has been converted under weakly acidic conditions to 2-methylamino-1*H*-imidazole-4,5-dione

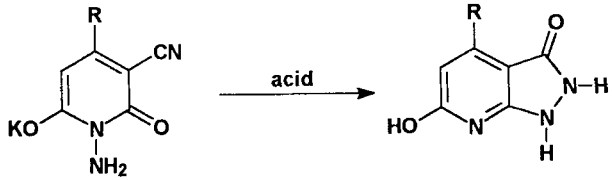


Scheme 28



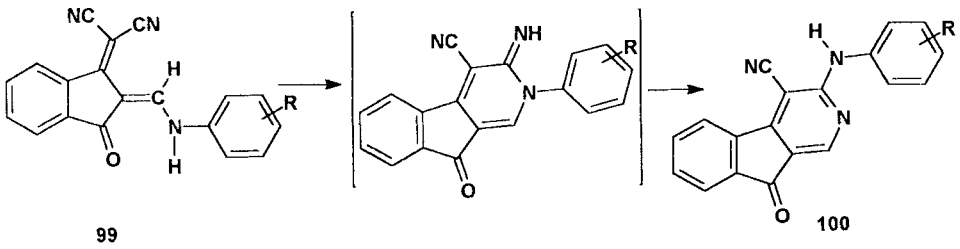
95 96

SCHEME 29



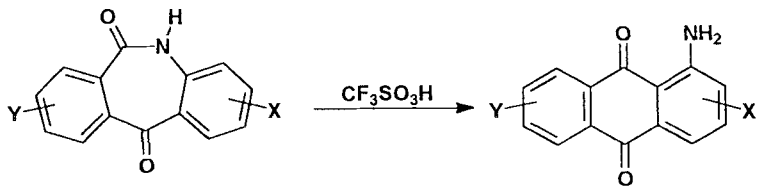
97 R = CF_3, CO_2Et 98

SCHEME 30

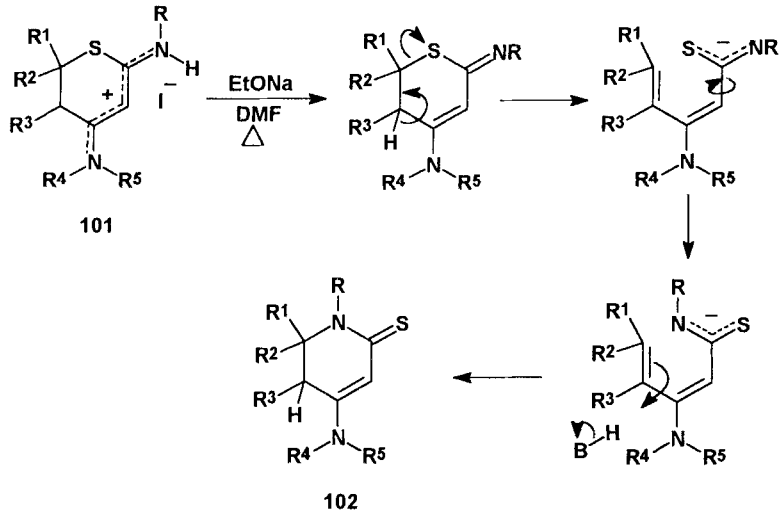


99 100

SCHEME 31



SCHEME 31A

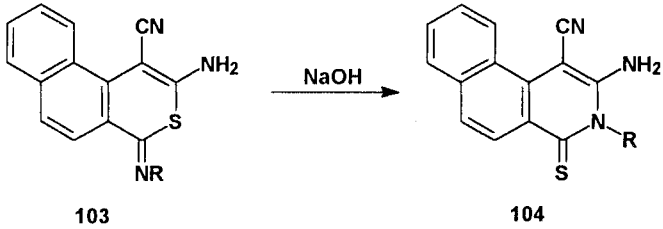


SCHEME 32

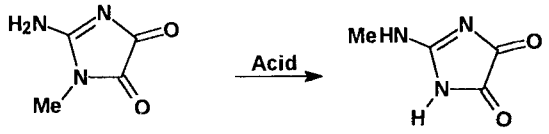
(**106**) (87BCJ4115). A basic ion exchange resin caused Dimroth rearrangement of some imidazole derivatives such as 4-amino-5-carboxamido-1,3-dimethylimidazolium *p*-toluenesulfonate [84IJC(B)870]. 5-Methylamino-imidazole-4-carboxylate underwent rearrangement with concentrated aqueous ammonia to give 5-amino-1-methylimidazole-4-carboxamide [79JCS(P1)3107] (Scheme 34).

2. *Thiazolines*

3*H*,6*H*-2,5-*Bis*(*p*-*N*,*N*′-dimethylaminophenyl)-1,2-thiazolino[5,4-*d*][1,2]-thiazoline-3,6-dithione (**107**) can be rearranged reversibly when catalyzed by Lewis acids or upon irradiation into the isomeric 3*H*,6*H*-3,6-*bis*(*p*-*N*,*N*′-dimethyl aminophenylimino)-1,2-dithiole (**108**) (90JPR387) (Scheme 35).



SCHEME 33



105 **106**

SCHEME 34

3. *Heterocycles with Sulfur and Selenium Atoms*

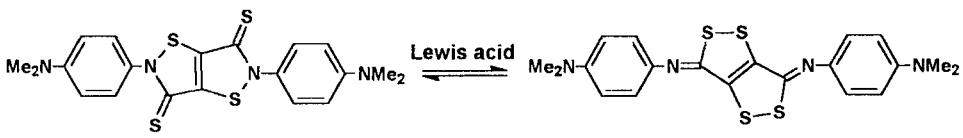
Heterocyclic thiones with one or two ring selenium atoms undergo Dimroth rearrangement during the lithiation-chalcogenation sequence, while the thione sulfur and one ring selenium atom exchange their places in **109** to give the 4,5-dithiolate **110** or the diselenolate **111.** Similarly, **112** gave 1,3-thiaselenole-2-selone-4,5-diselenolate **113** or **114.** Trapping experiments support the conclusion that this rearrangement took place during the lithiation step (92JOM213) (Schemes 36 and 37).

4. *Pyrimidines and Their Fused Analogs*

Most of the examples that were reported to experience a translocation process of one of the heteroatom substituents with one of the heteroatoms of the ring belong to pyrimidines and their fused ring systems.

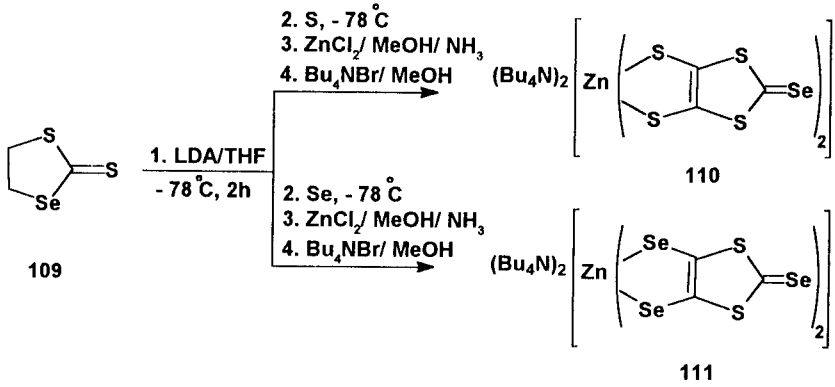
a. *Pyrimidines and Their Fused Rings with Saturated Carbocycles.* One of the early examples used to explain the mechanism of the rearrangement involved reacting $^{15}NH_3$ with 2-chloropyrimidine **115** to give the isotopically labeled **116.** Subsequent methylation gave **117** that was rearranged in alkali to **119** *via* **118.** Hydrolysis of **119** gave 2-hydroxypyrimidine **120,** which had the ^{15}N label in the ring [58AG400; 61NAT(L)828; 63CB534] (Scheme 38).

The conversion of **121** to **122** occurred through the addition of methylamine to **121,** which was claimed to have been recyclized with migration of

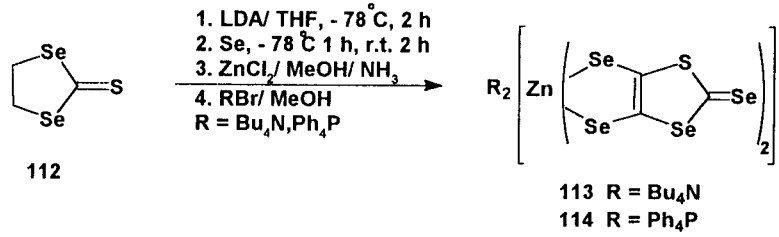


107 **108**

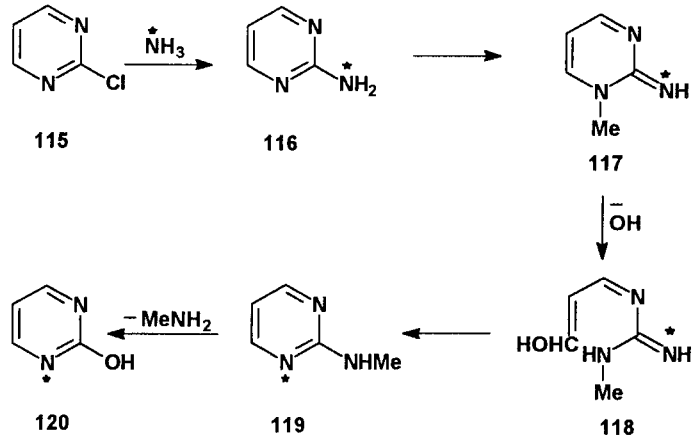
SCHEME 35



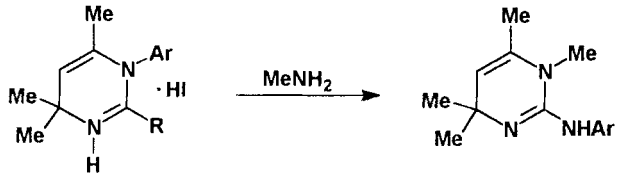
SCHEME 36



SCHEME 37



SCHEME 38



121 R = H, SMe **122**

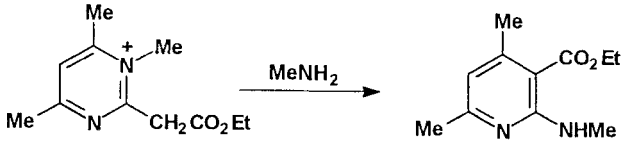
SCHEME 39

the *N*-phenyl fragment to the exocyclic position (76KGS561; 81MI2) (Scheme 39).

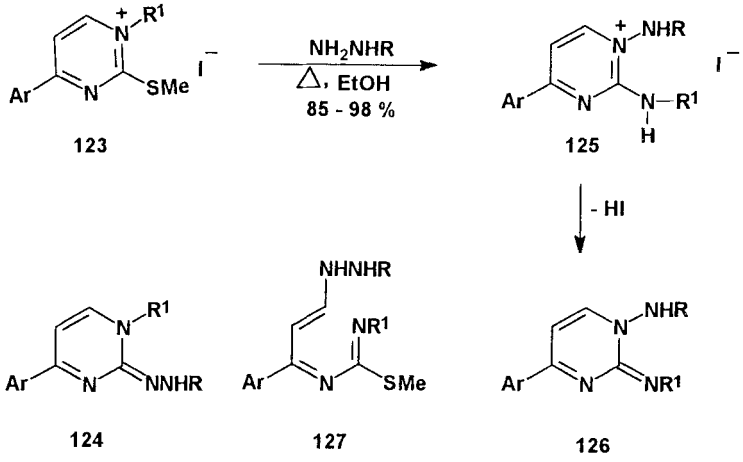
Rearrangement of the 2-ethoxycarbonylmethyl-1,4,6-trimethylpyrimidinium salt with alcoholic aqueous methylamine gave the respective 2-methylaminopyridine-3-carboxylate (94MI2) (Scheme 39a). Similarly, in alkaline medium, even nonquaternized 2-methyl-5-nitropyrimidine gave 2-amino-5-nitropyridine (94MI2) (Scheme 39A).

Reaction of 1-aryl-2-methylthiopyrimidinium iodide (**123,** R^1=Ar) with hydrazine or phenylhydrazine led to its rearrangement into 1-amino-2-arylaminopyrimidinium iodide **125** rather than the expected product **124** from a substitution reaction. Compound **125** can undergo deprotonation to give neutral substance **126** (90JHC1441). The structure of the 1,2-diaminopyrimidinium salts was proved by X-ray crystal analysis and spectral analysis (93JHC1607). The rearrangement of 1-amino-2-methylthiopyrimidinium iodide (**123,** R^1=NH_2) with hydrazines must follow an ANRORC mechanism (85T2237) involving, as an open-chain intermediate, the azatriene **127.** The hydrazine attacks position 6 of the educt **123,** giving after ring opening either isothiourea intermediate **127** or mostly substitution product **124,** which can be rearranged (Scheme 40).

1,2-Dihydro-2-imino-1-methylpyrimidine (**128;** R=R^1=R^2=H, R^3=Me) was not affected by aprotic triethylamine, whereas the rearranged product **131** was formed by the action of anhydrous diethylamine *via* the intermediates **129** and **130.** The rearrangement proceeded in three steps: amine addition, ring fission, and recyclization [68JCS(C)1452; 73RTC711;



SCHEME 39A



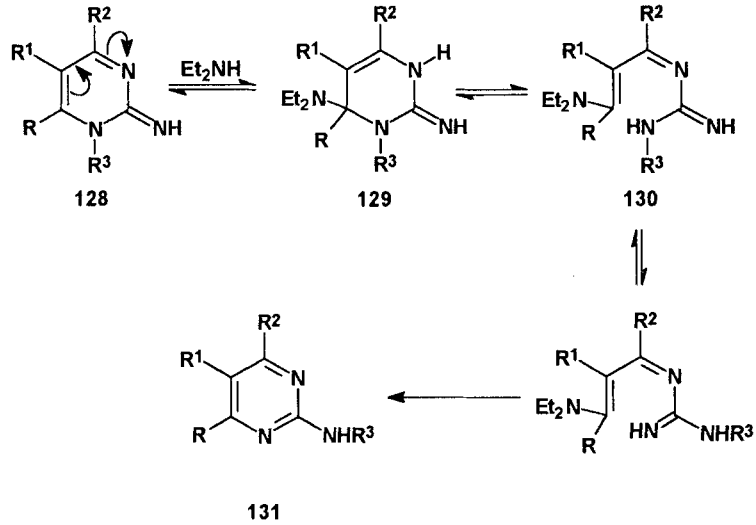
123 125 124 127 126

SCHEME 40

74JCS(P1)372]. Replacement of the 1-methyl group with higher *n*-alkyl homologs increased the rate of the rearrangement. This was attributed to a steric factor which hindered the reverse reaction of the acyclic imine intermediate **130** [67JCS(C)903].

The rate of rearrangement of **128** to **131** was facilitated by the presence of electron-withdrawing groups located at C5 or N1. Thus, the 1-allyl, 1-β-hydroxyethyl, 1-benzyl, and *p*-nitrobenzyl substituents increased the reaction rates, which caused an electron deficiency. Addition of electron-donating substituents to the parent ring decreased or even stopped the rearrangement (68MI1). The rates of Dimroth rearrangements of 1,2-dihydro-2-imino-1,4,6-trimethyl-5-substituted phenylpyrimidine indicated that, although the mesomeric effects of the *p*-substituents are attenuated by the presence of a considerable interplanar angle between the benzene and pyrimidine rings, rearrangement rates decreased in the order NO_2 > F > Cl > Br > Me > OMe > NH_2, following qualitatively the $p\sigma$-values for the groups. The rearrangement of 1,2-dihydro-2-imino-1,6-dimethylpyrimidine took place more rapidly than its 1,4-dimethyl isomer, and the rate of 1,2-dihydro-2-imino-5-methoxy-1-methylpyrimidine was greater than that of the parent imine [63JCS1276; 71JCS(C)250] (Scheme 41).

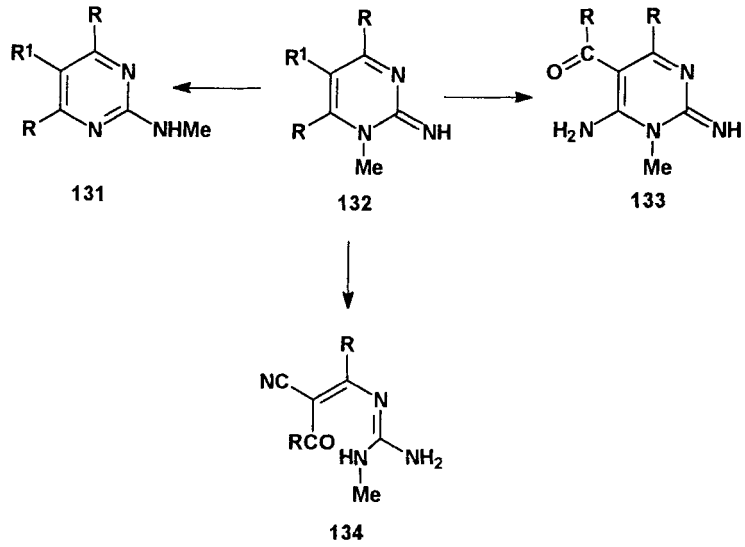
5-Cyano-1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine (**132;** R=Me, R^1=CN) rapidly underwent rearrangement under mild alkaline conditions to yield 5-cyano-4,6-dimethyl-2-methylaminopyrimidine (**131;** R=Me, R^1=CN). However, the imine (**132;** R=H, R^1=CN) afforded a normal rearranged product (**131;** R=H, R^1=CN) at pH 5–9 and an abnormal one (**133;** R=H) at higher pH values. The dimethyl homolog **132** (R=Me,



SCHEME 41

R^1=CN) failed to produce **133** (R=Me) even in strong alkali. The difference in behavior between these homologs may result from the ability of the aldehyde group of the intermediate (**134;** R=H) to form the hydrate in alkali. This would discourage normal recyclization by elimination of water and encourage abnormal cyclization by addition to the cyano group. In case of the intermediate (**134;** R=Me), the keto group would form such a hydrate much less readily and normal recyclization rearrangement of the imine (**132;** R=Me) would occur [66JCS(C)164]. A less electron-withdrawing group than that of the cyano group, such as the 5-carbamoyl substituent, caused the 5-carbamoyl-1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine hydroiodide to be isomerized faster in alkali to the amine (**131;** R=Me, R^1=$CONH_2$). Also the 5-halogenated imines (**132;** R=Me, R^1=Cl or I) rearranged at a rate intermediate between that of the parent imine (**132;** R=H, R^1=Cl or I) and its 5-carbamoyl derivative [67JCS(C)903] (Scheme 42).

The pK_a values and UV spectra of imines **135** and their respective methylamino isomers **136** indicated that the rearrangement can be progressively followed spectrometrically at pH 13. The rate of rearrangement varied widely with nature, number, and position of the C-alkyl substituents [63JCS1276; 67JCS(C)1928; 71JCS(C)250; 75H283]. The presence of a 5-alkyl group slowed the rearrangement; a 4- or 6-alkyl group caused much less retardation. However, in **135** (R^1=R^2=Me, R^3=H) and **135** (R^1=R^2 =H, R^3=Me) there was a small increase in rate on adding a methyl



SCHEME 42

group such as in **135** (R^1=R^2=R^3=Me) and **135** (R^1=H, R^2=R^3=Me), respectively. Moreover, the relative effects of the methyl, ethyl, and isopropyl groups in the 2- or 4-positions followed no fixed order. The marked effect of the 5-alkyl group was due to a combination of mesomeric electron enrichment at C2, which discouraged the OH^- attack, probably the first step in a Dimroth rearrangement (65JCS7071), and the steric hinderance to the 180° rotation about the 5–6 bond (**A** to **B**), a necessity for recyclization to **136.** The relatively minor effect of a 4-alkyl group on rearrangement appeared to arise from minimal mesomeric and inductive effects on C2 coupled with the lack of any steric factor. In contrast, the similarly minor effect of a 2-alkyl group seemed to be the result of several competing factors: inductive electron enrichment at C2, steric hindrance to hydroxy approach, 1–2 bond instability from crowding in the N1/C2 area following hydroxylation, and steric favoring of the required conformation **B** in the equilibrium (**A** ⇌ **B**) [74JCS(P1)372]. The mass spectral fragmentation patterns of **135** (R^1=R^2=R^3=H or R^1=R^3=H, R^2=Me) were found to be identical to those of the corresponding **136** as a consequence of their rearrangement upon electron bombardment (75H283).

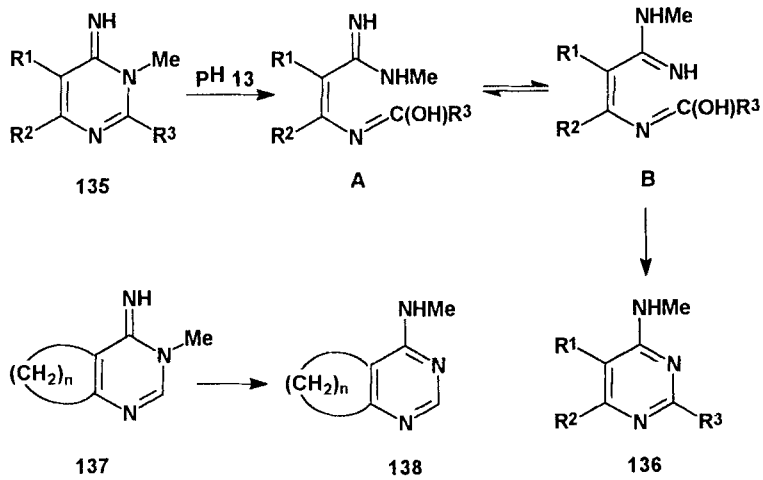
The tetramethylene derivative (**137;** n=4) rearranged at a rate comparable with that of the 4,5-dimethyl analog **135,** but the trimethylene derivative (**137;** n=3) did so eight times faster. There are two factors involved; the mild strain, introduced by annulation of the five- (but not the six-) membered

ring, tends to elongate (destabilize) the 2–3 bond and after fission of the 2–3 bond, there is less steric hindrance for **137** (n=3) than in that from **137** (n=4) to give **138** [74JCS(P1)372] (Scheme 43).

1,6-Dihydro-6-imino-1-methylpyrimidine (**135;** R^1=R^2=H) rearranged faster than its 1,2-dihydro-2-imino isomer (**128;** R=H). The 1,6-dihydro-6-imino-1-methyl-2-methylthiopyrimidine (**135;** R^1=H, R^2=SMe) failed to rearrange due to the difficulty of water addition to the N-1–C-2 bond because of steric hindrance by the thioether group. The same group at C4 had no such effect [71JCS(C)2507].

Uracil derivatives possessing an electron-withdrawing group at the 5-position are remarkably sensitive to nucleophilic attack on the 6-position (77CSR43) and frequently undergo various types of ring transformations [81JOC3949; 83JCS(P1)1293; 84JCS(P1)1859; 85JCS(P1)1137, 85JOC1512; 90JCS(P1)123, 90JCS(P1)367]. Although, 6-aminouracil derivatives are generally inactive toward nucleophiles, a phenyl group at the 1-position facilitates the cleavage of the N1–C2 bond by attack of hydroxide ion on the 2-position and consequently induces Dimroth rearrangement [89JCS(P1)1695; 90T3431].

The reaction of 1-substituted-4,4,6-trimethyl-1,4-dihydropyrimidine-2(3*H*)-thiones **139** with 11 *M* HCl was temperature dependent and the rearrangement results at lower temperature via the dehydrative recyclization of the initial hydrolytic product involving attack of the thioureido sulfur on the carbonyl carbon to give 2-substituted amino-4,4,6-trimethyl-4*H*-1,3-thiazines **140** [80JCS(P1)1013]. On the other hand, intramolecular ther-



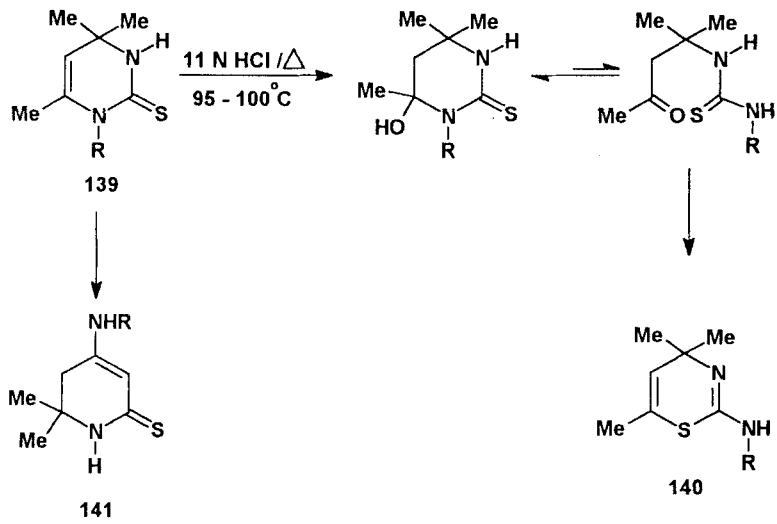
SCHEME 43

mal rearrangement of **139** gave 4-substituted amino-6,6-dimethyl-5,6-dihydropyridine-2(1*H*)-thiones **141** in a molten state, constituting a unique Dimroth rearrangement [91IJC(B)740; 92IJC(B)142] (Scheme 44).

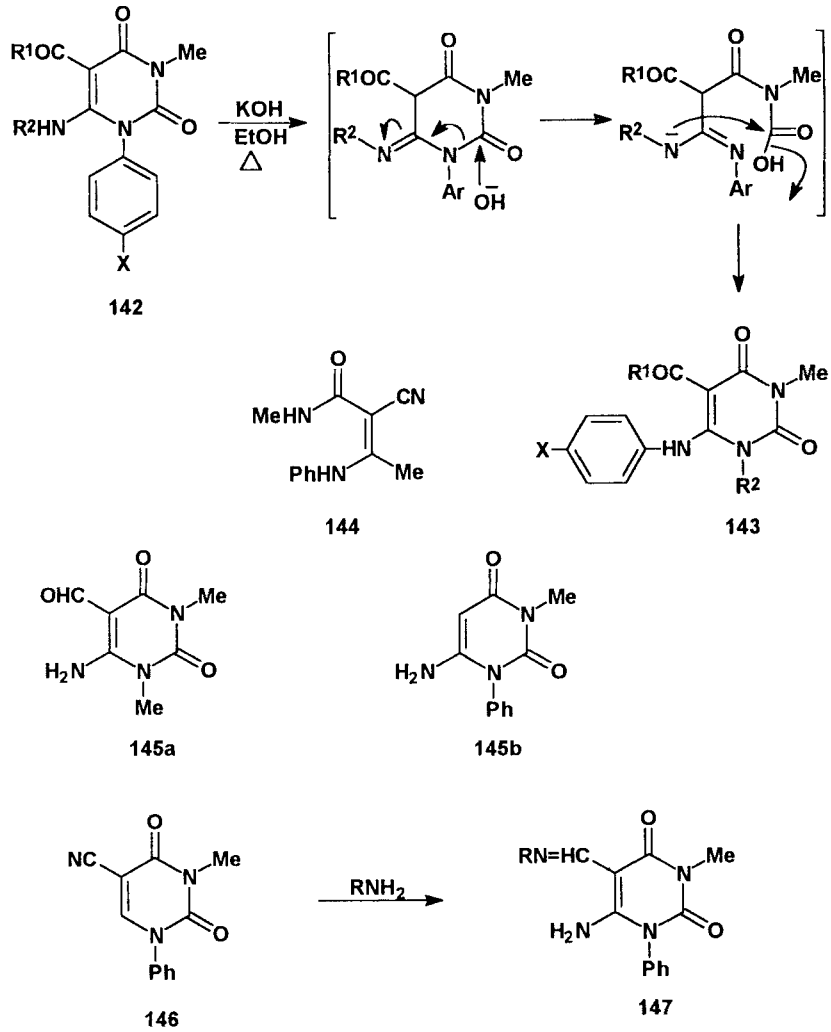
The reaction of 6-amino-1-aryl-5-formyl(acetyl)uracil (**142**) with potassium hydroxide in boiling ethanol resulted in Dimroth rearrangement to give 6-anilino-5-formyl(acetyl)uracil (**143**) (92CPB2839). However, the parent derivative 5-acetyl-6-amino-3-methyl-1-phenyluracil (**142**) gave upon similar treatment the rearranged product **143** in addition to the 2-anilino-3-cyano-*N*-methylcrotonamide (**144**). However, 6-amino-5-formyl-1,3-dimethyl uracil (**145a**) and 6-amino-3-methyl-1-phenyluracil (**145b**) did not undergo the Dimroth rearrangement, which indicated that both the N-1 phenyl group and the 5-acyl group on the uracil ring must be present for rearrangement to occur.

Reaction of 5-cyano-3-methyl-1-phenyluracil (**146**) with amines induced rearrangement, instead of an N1 exchange reaction, to give 6-amino-3-methyl-1-phenyl-5-(N-substituted iminomethyl)uracil (**147**) (89CPB2008) (Scheme 45).

Dimroth rearrangement of 1,6-dihydro-6-imino-1,2-polymethylenepyrimidines (**148**) provided a route to 6-aminopyrimidines **149**, bridged by a polymethylene chain between the amino group and the original 2-position. The rate of rearrangement was enhanced by using substrates **148** bearing an electron-withdrawing group (R=CN, $CONH_2$, or CO_2Et) adjacent to the imino group (75AJC119). A lengthy seven-membered polymethylene chain

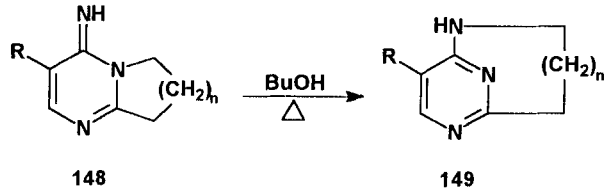


SCHEME 44



SCHEME 45

in the imines **148** presented no hindrance to the formation of the required bridge during the rearrangement to products **149.** By contrast, a six-membered chain rearranged slowly, while a four- or five-membered chain was too short to serve as a bridge and hence hindered rearrangement (Scheme 46).

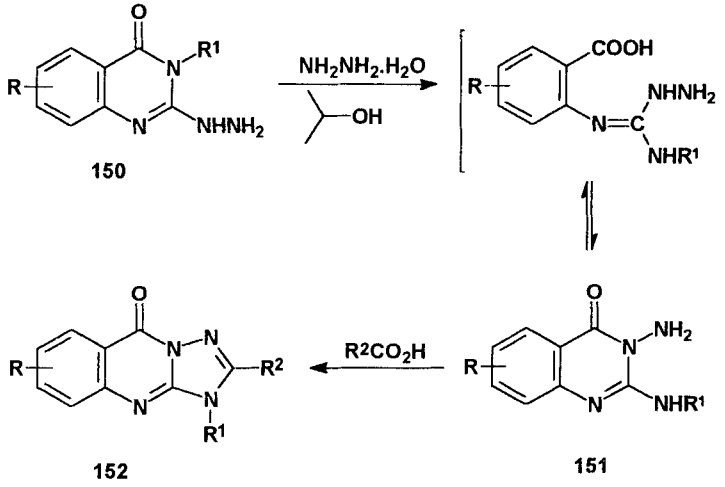


148 149

SCHEME 46

b. *Quinazolines.* Substituted 3-alkyl and 3-aryl-2-hydrazino-4(3*H*)-quinazolinone (**150**) underwent Dimroth rearrangement to give 3-amino-2-alkyl(aryl)aminoquinazolinone (**151**) (85PHA54; 87PHA412; 90PHA30) when heated in hydrazine hydrate and isopropyl alcohol. When the hydrazine **150** was heated with carboxylic acids, it gave **152** (91MI1). It was proposed that **150** rearranged to the diaminoquinazolinone **151,** which underwent cyclocondensation *in situ* with the carboxylic acids to give **152** (Scheme 47).

2,3-Dihydro-2-imino-3-methylquinazoline (**153a**) rearranged completely into 2-methylaminoquinazoline (**154a**) in 1 *N* alkali at room temperature, more rapidly than its 5-,6-, and 7-methoxy derivatives. An increase in alkalinity caused an increase in the rate especially for **153a** and its 6-methoxy derivative. When the rate was measured at pH 12.5, the 5-methoxy derivative rearranged faster than the simple imine **153a,** whereas the 6- and 7-methoxy imines did so 3–4 times more slowly (68AJC2813).



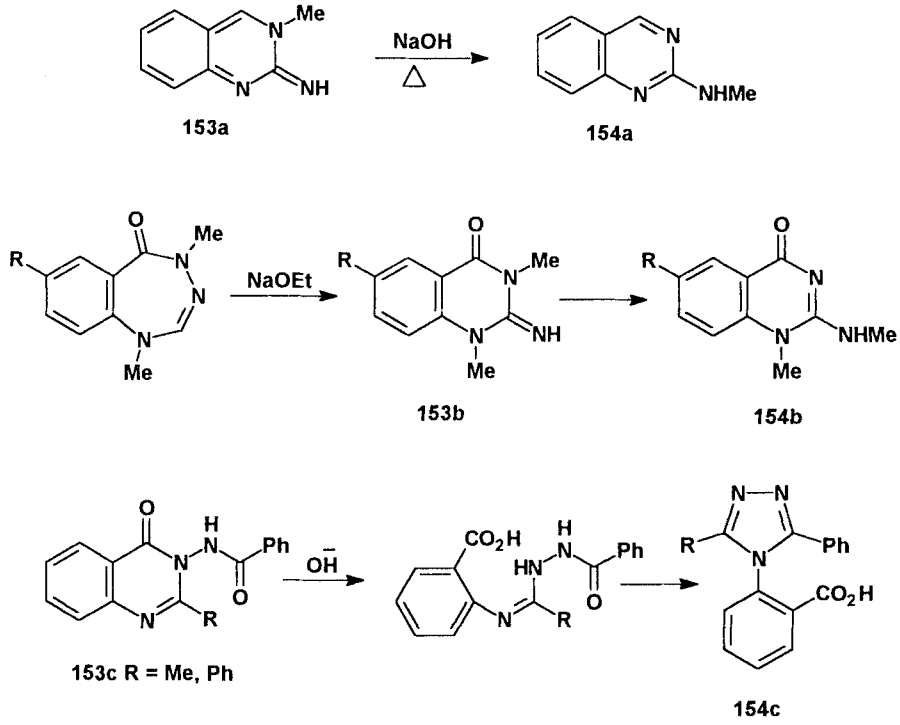
150 152 151

SCHEME 47

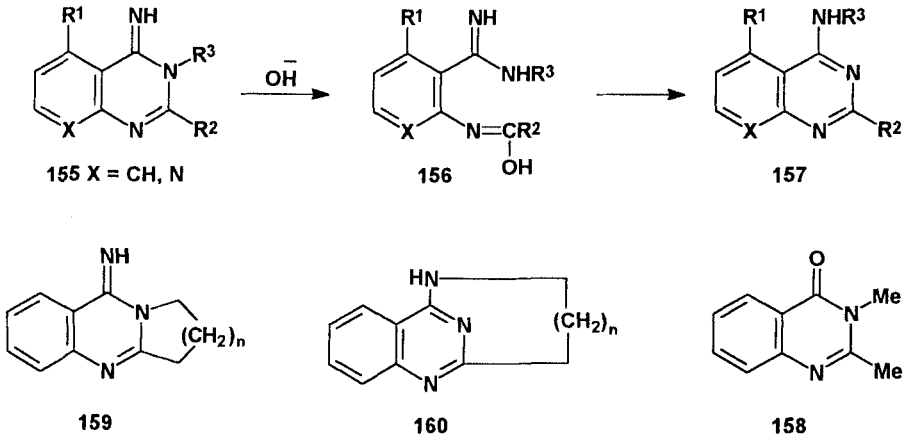
Ring contraction of 1,4-dihydro-1,3,4-benzotriazepin-5-ones by the action of NaOEt gave 1-methyl-2-methylamino-4(1*H*)-quinazolinones **154b** via rearrangement of 1,3-dimethylquinazolinone-3-imines **153b** (78JOC 3427).

2-Blocked 3-benzamidoquinazolin-4-one **153c,** on treatment with dilute alkali, gave the triazole **154c** arising from 3–4 bond cleavage followed by cyclization (86T4481) (Scheme 48).

3-Alkyl-3,4-dihydro-4-iminoquinazoline **155** rearranged in alkali to 4-aminoquinazoline **157,** except for the derivative **155** (R^1=H, R^2=R^3=Me, X=CH), where some hydrolysis also occurred to give the quinazolinone **158** [75JCS(P1)2182; 91MI3]. Imines bearing bulky branched *N*-alkyl groups rearranged more slowly than the *N*-methyl homolog. This was attributed to steric hindrance toward the hydration of the 2–3 bond prior to its fission to yield the intermediate **156,** which was consistent with the decrease in rearrangement rate found by the presence of a 2-methyl group in **155.** Steric interference between the bulky group R^3 and the *ortho* hydro-



SCHEME 48



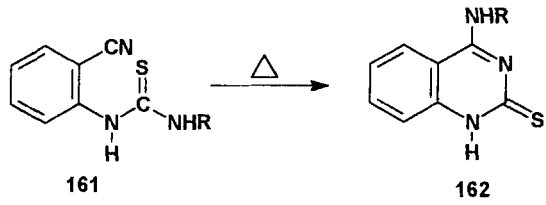
SCHEME 49

gen atom (R^1) in the intermediate **156** was inconsistent with the increase in the rate when a 5-methyl group was present; it could, however, result from instability resulting from steric interference between the imino- and the 5-methyl group in **155** [75JCS(P1) 2182].

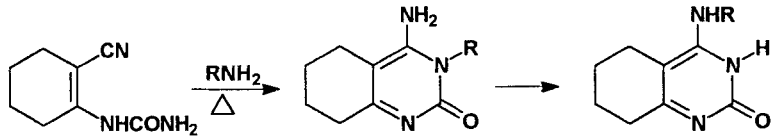
Rearrangement of the pentamethyleneimine (**159;** n=3) proved impossible because the chain was too short to form a stable bridged amine (**160;** n=3). For the same reason the rearrangement of the imine (**159;** n=4) was very slow. However, the higher homologs (**159;** n=5 or 7) rearranged satisfactorily [75JCS(P1)2182] (Scheme 49).

2-(3-Thioureido)benzonitrile **161** rearranged thermally or in boiling aqueous DMF to give 1,2-dihydroquinazoline **162** (92MI2). Similarly, the ureido derivative **163** gave **164** upon heating with amines via a Dimroth rearrangement of an aminohydroquinazolinone (88JPR289) (Schemes 50 and 51).

When 2-phenyl-1-unsubstituted quinazoline 3-oxide **165** was heated in a solvent (xylene, toluene, butanol, or ethanol) or melted, it gave the oxime



SCHEME 50



163 **164**

SCHEME 51

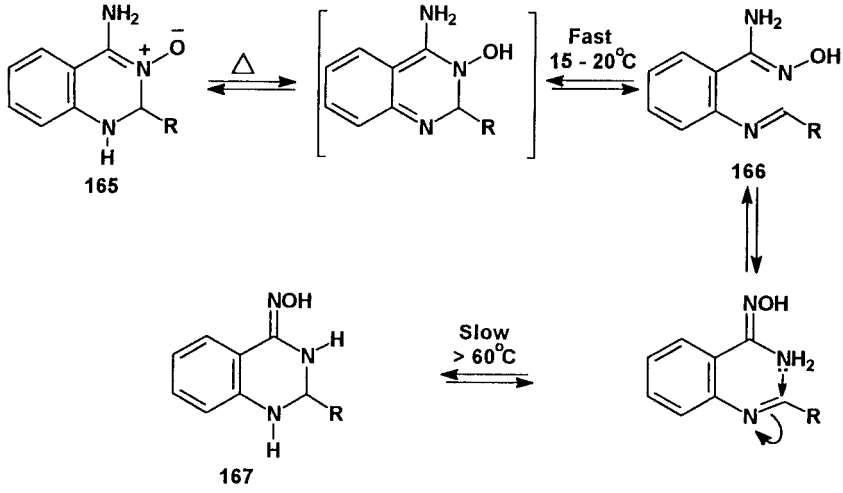
167 through intermediate **166.** No catalyst was needed and no solvent effect was found. The 2-alkylquinazoline-3-oxides isomerize much slower than the 2-phenyl and 2-styryl analogs. They can be transformed to the oxime **167** by continueous heating in butanol [86JCS(P1)2163]. The transformations proceed by an addition–elimination mechanism in the presence of acidic or basic catalysts (67JOC1151) or an acylating agent (65JOC2766). The primary product is a Schiff base **166** which is transformed at room temperature in a fast but reversible electrocyclic ring closure and proton migration to the nitrone **165** (R=Ph). At higher temperature the formation of the thermodynamically more stable semicyclic amidoxime (**167;** R=Ph) is favored. The process involves reversion to **166** by proton migration and cleavage of C2–N3 bond of the quinazoline ring, followed by rotation and recyclization.

The conversion of 4-amino-1*H*-quinazolin-2-one 3(*N*)-oxide (**168**) to 4-oximino-1*H*, 3*H*-quinazolin-2-one (**169**) by heating in a solution of DMF is an example of a Dimroth rearrangement in which the hydroxy group (or the *N*-oxide oxygen atom) acts as the substituent on the amidine system (81KGS1264). The 3-*N*-monoalkylated salt of 4-aminoquinazoline **170** also underwent the rearrangement to give **171** (85TL2905) (Schemes 52, 53, and 54).

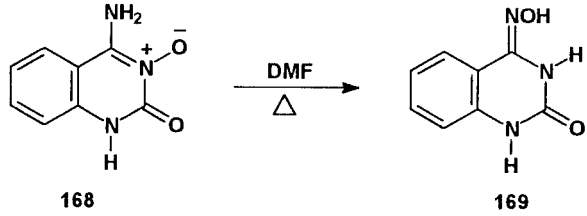
c. *Pyrrolopyrimidines.* The hydrochloride salt of 4-amino-3-substituted-7*H*-pyrrolo[2,3-*d*]pyrimidine (**172**) can be rearranged to the corresponding isomer **173** (81CB2056; 84MI1) (Scheme 55).

d. *Furopyrimidines.* Furo[2,3-*d*]pyrimidin-4(3*H*)-imine **174** underwent Dimroth rearrangement to the thermodynamically more stable 4-arylamino compound **175** by heating in water (85CS227; 86CS337) or aqueous dioxane (93KGS124). The rearrangement of the benzofuro[3,2-*d*] isomers to their 4-substituted amino derivatives was also observed [80IJC(B)115; 86CB1070] (Scheme 56).

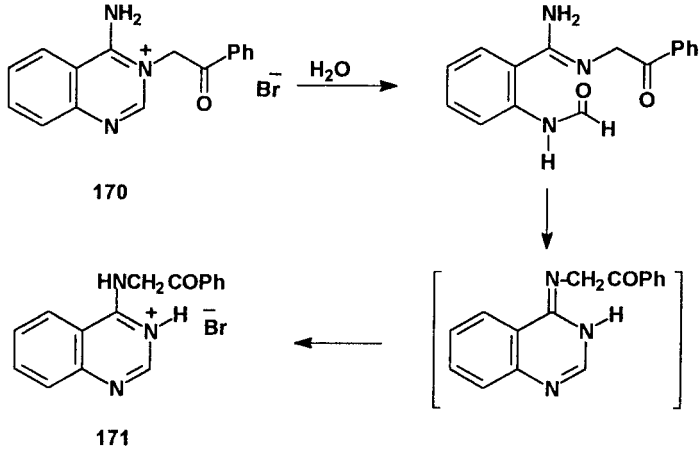
e. *Thienopyrimidines.* Substituted iminobenzothienopyrimidine **176** has been rearranged, under base catalysis, to the benzothienopyrimidine **177**



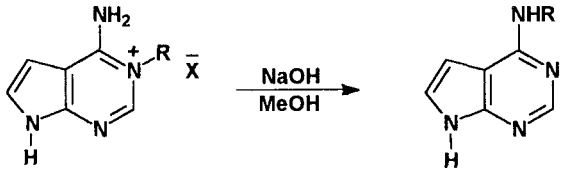
SCHEME 52



SCHEME 53



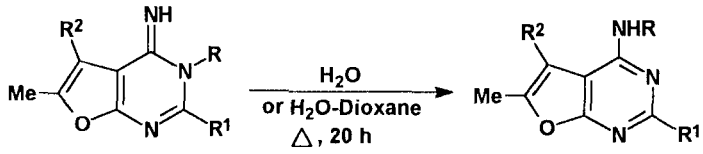
SCHEME 54



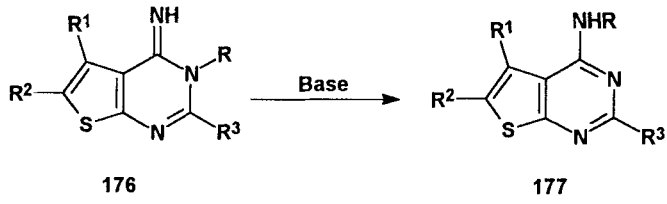
SCHEME 55

[88CS195; 90IJC(B)1070, 90IJC(B)1074, 90JIC260; 92MI1]. An amino group at position 2 as in 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidines (**178**) directed the rearrangement to involve the ring opening and recyclization to give **179** where the *N*-aryl group moved to position 2. Thus, sodium ethoxide in ethanol at 40–50°C caused the isomerization of **178** to about 50%, but no isomerization occurred under acidic conditions (10% HCl, PTSA/C_6H_6, HCO_2H). The rearranged product 4-amino-2-arylaminothieno[2,3-*d*]pyrimidine (**179**) may be formed by a reaction pathway involving the cleavage of the C4–N3 bond followed by a free rotation around the C2–N1 bond of the resulting intermediate and then recyclization (93JHC435). 2,3-Polymethylenethieno[2,3-*d*]pyrimidin-4-imine derivatives underwent Dimroth rearrangement to give the corresponding heterocondensed pyrimidophane derivatives (86CB1070) (Schemes 57 and 58).

f. *Pyrazolopyrimidines.* The hydrolytic rearrangement of pyrazolo-[3,4-*d*]pyrimidine **180** gave the isomeric derivative **181** (60JA3147). Condensation of N-substituted amides with 5-amino-1-methylpyrazole-3,4-dicarbonitrile (**182**) gave 4-alkylamino-1-methylpyrazole[3,4-*d*]pyrimidine-3-carbonitrile (**185**), which was apparently formed via intermediate **183.** The formation of **185** from **183** occurred via a Dimroth rearrangement in an anhydrous medium [73JCS(P1)1903]. Species **183** is an obligatory intermediate in the Dimroth rearrangement and once formed may, according to the reaction conditions, be dehydrated to afford the 5-substituted pyra-

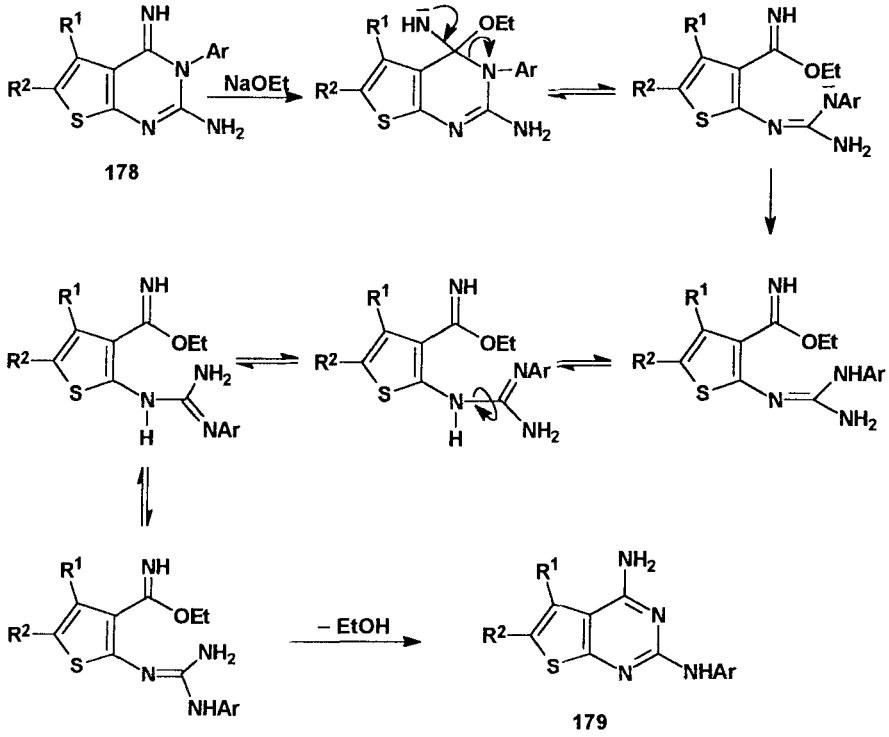


SCHEME 56

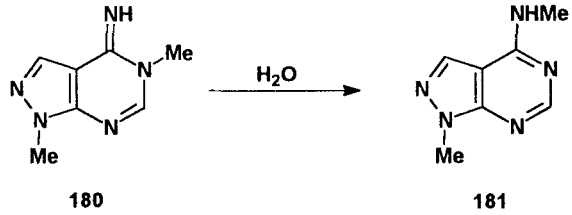


SCHEME 57

zolo[3,4-*d*]pyrimidine **184** or complete the rearrangement to give the 4-substituted pyrazolo[3,4-*d*]pyrimidine **185.** The conversion of **183** to **185** could be partially hindered by carrying out the reaction in the presence of molecular sieves. This effectively eliminated the equilibrium between **183** and **184** and resulted in the formation of both **184** and **185.** In absence of the dehydrating agent, only **185** was formed (Schemes 59 and 60).



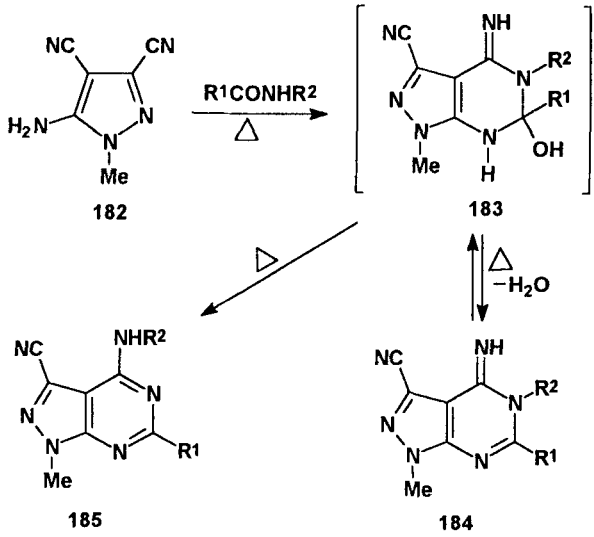
SCHEME 58



180 **181**

SCHEME 59

g. *Adenine analogs.* A number of studies were done on the Dimroth rearrangement of 1-alkyladenine and its derivatives to produce isomeric 6-N-substituted derivatives [73B2179, 73B4074, 73JOC2247; 74CPB2211; 77MI1; 78BRP1534163; 80MI1; 81MI1; 82JAP(K)57/139094; 83JPT113; 85CPB3635; 86JHC1189; 87CPB4482]. The rearrangement of 1-methyladenosine **186** to *N*-methyl adenosine **188** occured without isolation of intermediates (68B3453). However, the 1-alkoxyadenine derivative **186** rearranged to the 6-*N*-alkoxy isomer **188** through isolable monocyclic intermediate **187** [66CI(L)1967; 69CPB1128, 69JCS(CC)458; 71CPB1731, 71T2415; 72JMC182, 72T535; 73JCS(CC)917; 74CPB2211]. The mechanism of rearrangement of **186** may involve a rate-determining initial ring opening caused by attack of hydroxide ion on both the protonated and the neutral species of **186** at position 2 and a subsequent fast ring clo-



182 **183** **185** **184**

SCHEME 60

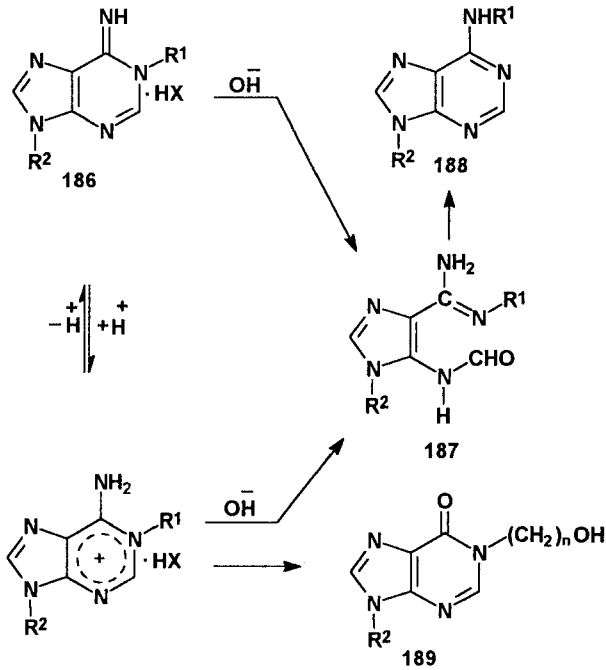
sure of the intermediate **187** (90CPB3326). At pHs 7.6 and higher at 40°C, **186** (R^1=R^2=Me) rearranged more rapidly than the 1-methoxy-9-methyladenine, although the later underwent ring opening 30 times as fast as the former (72T535). The enhancement of the ring-opening step and the slowing down of the recyclization step for the 1-methoxy derivative could be attributed to the electron-withdrawing nature of the substituent at position 1. A comparison of rate constants [63BJ127; 68B3453, 68JCS(C)2026; 72JA(94)8542; 85CPB3635] for the rearrangement of **186** (R^1=Me; R^2=β-**D**-ribofuranosyl) and its analogs at various temperatures and pHs with those of **186** (R^1=R^2=Me) has suggested that the β-**D**-ribofuranosyl group at the 9-position may have a rate-promoting effect (72T535) due to the electron-withdrawing effect of the furanose ring oxygen that accelerates the attack of the hydroxide ion (75CPB54; 85CPB3635, 85MI1). The intramolecular participation of the 5′-OH group may have a certain role to play in the acceleration of ring opening. An electron-withdrawing group at the 1-position and the ribofuranosyl group at the 9-position separately lower the pK_a of **186** and this causes the population of the reactive protonated species at near neutrality to decrease [52BBA369; 59JA178; 60JA222; 63BJ127; 67B3625; 72JA(82)4708; 75CPB54].

Kinetic studies on the rearrangement of a series of 1-alkyl-9-methyladenines and 1-alkyladenosines in aqueous solution (75CPB54) indicated that the rate increase as the pH of the medium increased. At pHs 10 and below the *n*-alkyl homologs underwent rearrangement at comparable rates, whereas at pHs 11 and above the 1-ethyl and 1-propyl derivatives rearranged more slowly than did the 1-methyl derivative. The 1-benzyl derivative underwent rearrangement faster than the 1-methyl derivative at pHs 10 and below, whereas raising the pH to 11 and above reversed the order. The most susceptible compound to rearrangement was nucleoside **186** (R^1=Bn; R^2=β-**D**-ribofuranosyl), as a result of a balance of steric and electronic effects, but at pHs 10 and above it was nucleoside **186** (R^1=Me; R^2=β-**D**-ribofuranosyl) which possessed the smallest alkyl group at the 1-position (75CPB54).

The protonated species of the 1-benzyl analog rearranged faster than any of the 1-alkyl-9-methyladenines. In contrast, the neutral species rearranged only at an extremely slower rate (75CPB54). Hydroxide ion attacked the protonated species much faster than the neutral species and the former was influenced by an electroic factor for the 1-substituent and the later by a steric factor. In the reaction of the neutral species for larger *n*-alkyl groups at the 1-position retarded the attack by hydroxide ion at the 2-position owing to their steric bulk (75CPB54). The roughly similar rates for the reaction of the protonated *n*-alkyl homologs and the rate enhancement observed for the protonated 1-benzyl derivatives suggested that the

electron-withdrawing property of the 1-benzyl group affects hydroxide attack on the protonated species at the 2-position more significantly than does its steric bulk. The β-**D**-ribofuranosyl group at the 9-position accelerated the ring opening of both the neutral and protonated species (Scheme 61).

A rate study on the rearrangement of a series of 9-substituted 1-(ω-hydroxyalkyl)adenosines **186** and related compounds (X=Br or ClO_4) indicated that an unusual hydrolytic deamination occurred competitively with the Dimroth rearrangement at near-neutrality to give **189** instead of the 6-N-substituted isomer **188** (86CPB1094). The 1-(ω-hydroxyalkyl) analogs **186** [R^2=Et, R^1=$(CH_2)_2OH$ or $(CH_2)_3OH$] as hydrobromide salts rearranged faster than the corresponding 1-alkyl analogs **186** (R^1=Et, R^2=Et or Pr) as perchlorates. This rate enhancement was due to the electron-withdrawing effect and not to the intramolecular participation of the hydroxy group in the 1-position. In the reaction of neutral species, hydroxide attack may be influenced by the steric bulk of the 1-substituent. The relative rate of hydrolytic deamination of **186** [R^2=Et, R^1=$(CH_2)_2OH$



SCHEME 61

or $(CH_2)_3OH$] as HBr and $HClO_4$ salts with respect to Dimroth rearrangement increased as the pH of the reaction medium decreased.

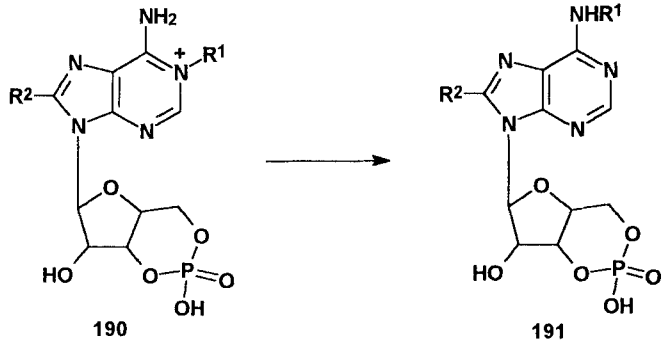
The Dimroth rearrangement of **190** (R^1=$OCH_2CH_2NH_2$, R^2=H or Br) was rationalized in terms of intramolecular catalysis by the aliphatic amino group in the substituent to give **191** (79MI2) (Scheme 62).

Treatment of 1-ethyladenine **192** with 0.2 *N* aqueous NaOH caused rearrangement to *N*-ethyladenine **194** with two by-products, hypoxanthine **196** and 1-ethylhypoxanthine **198,** resulting from unusual hydrolytic deaminations of the intermediate **193** via **195** and **197,** respectively. Rates increased with an increase in the pH of the medium. Similar results were also reported for the rearrangement of 7-alkyl-1-methyladenines (94CPB382) (Scheme 63).

1,9-Diethyladenine hydrobromide **199,** when treated with triethyl phosphite, produced the diethyl isomer **200** by Dimroth rearrangement (76CPB655; 86CPB1094) in contrast to the alkylations of 1,9-disubstituted adenines with common alkylating agents in which alkylations occurred predominantly at the N6 position (74B1913; 76CPB655; 83CPB3149). Also, the adenine derivative **201** was rearranged to **202** (93CPB453) (Scheme 64).

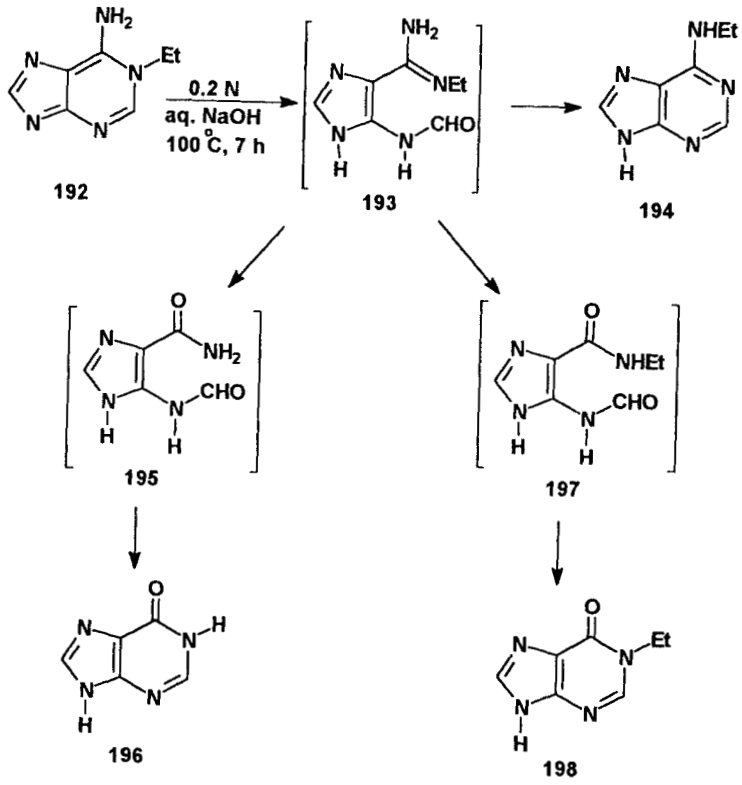
6-N-Alkylated derivatives of adenine nucleotide coenzymes such as NAD and ATP were synthesized by the Dimroth rearrangement of 1-N-alkylated adenine nucleotides (81ABC2631). The rearrangement occurred with better efficiency by using anion exchange resins (OH form) in which high concentrations of OH^- ions around the adsorbed nucleotide molecules existed.

Phosphorylation of **203** by using 2-methylthio-4*H*-1,3,2-benzodioxaphosphorin-2-oxide (MTBO) in the presence of 4-morpholine-*N*,'*N*-dicyclohexylcarboxamidine as a catalyst gave **204** that rearranged to **205** (86MI3; 91ABC1999) (Scheme 65).

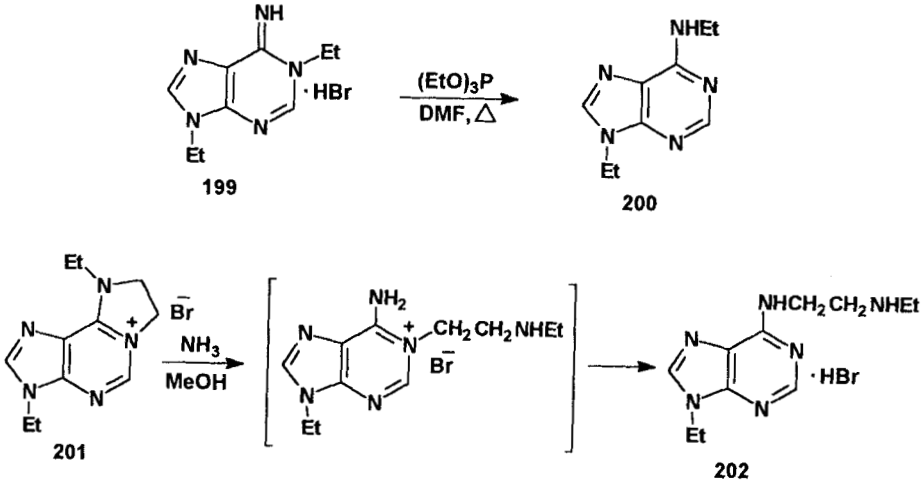


190 191

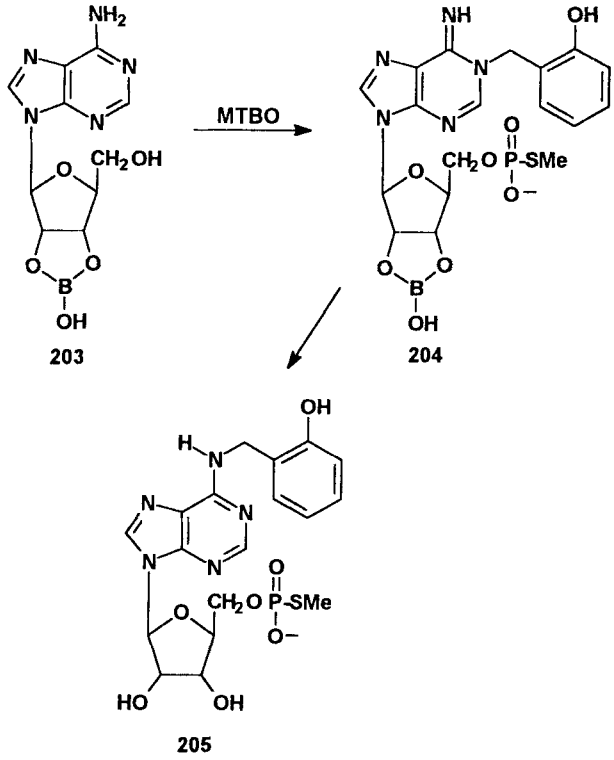
SCHEME 62



SCHEME 63



SCHEME 64



SCHEME 65

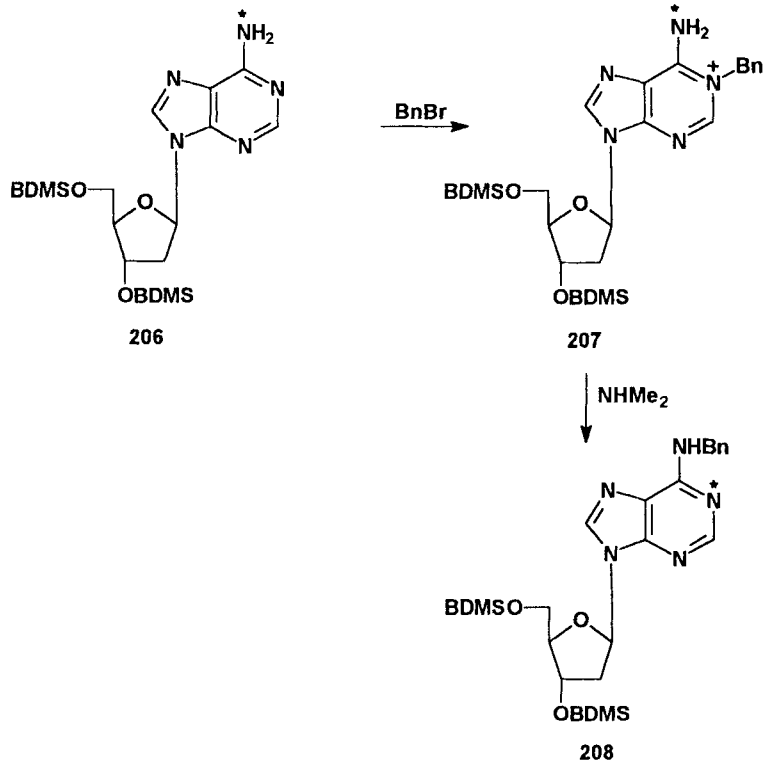
The mechanism of the Dimroth rearrangement of adenosine was determined by using labeled ^{15}N to follow the exchange between the exocyclic and endocyclic positions in the adenine ring. The elucidation of this rearrangement by NMR indicates that ring cleavage between the N1 and C2 atoms followed by internal rotation is the correct pathway (75BBR581; 77CB373).

Deoxyadenosine when protected as the 3′,5′-*O*-*bis*(*tert*-butyldimethylsilyl) (BDMS) derivative **206** and reacted with benzyl bromide gave **207,** which underwent the rearrangement using methanolic dimethylamine (1:1) to give **208** (73B2179). Labeling at position 1 was achieved via Dimroth rearrangement and the ^{15}N-label can be used as a ^{15}N NMR probe (87JA1275). 1-Methyl purinium ribonucleoside cation **209** in aqueous ammonia was converted to purine nucleoside **210** in a reaction which involved addition of ammonia at C6 followed by a rearrangement with elimination of methylamine. This reaction offered a method for specific incorporation of ^{15}N into heterocyclic compounds (90JA1247). In ammonia buffers of

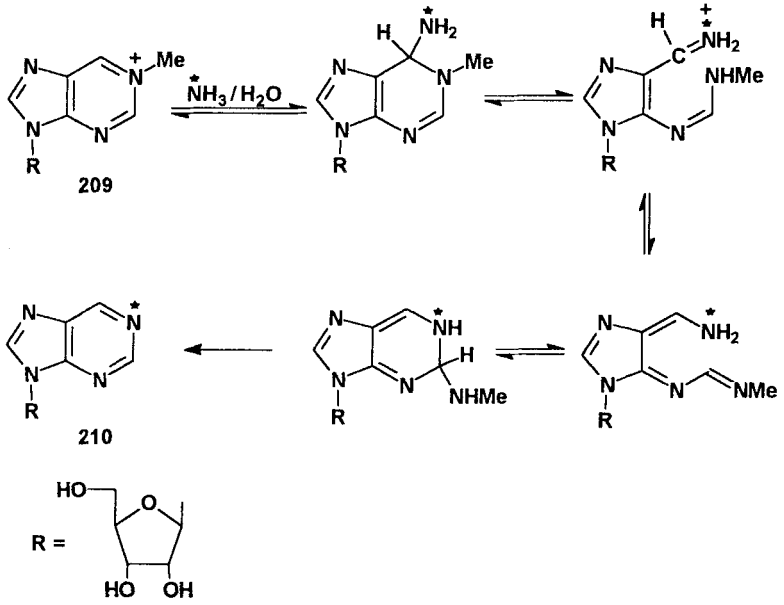
varying pH, the velocity of this reaction was found to reach maximum near pH 10 (90JA1247) (Schemes 66 and 67).

The 4-nitrophenyl group at position 1 of 2′-deoxyinosine not only served as an electron-withdrawing group to increase the electrophilicity of the C-2 position but it also served as a good leaving group following ring closure of the formamidine intermediate. Thus, an ^{15}N atom can be incorporated in the hypoxanthine base by direct reaction of $^{15}NH_3$ with the 1-(4-nitrophenyl)-3′, 5′-diacetyl-2′-deoxyinosine to give the [1-^{15}N]-2′-deoxyinosine and the 5-amino-1-(2′-deoxy-β-**D**-ribofuranosyl)imidazole-4-[*N*-(4-nitrophenyl)carboxamide] (Scheme 67a). The use of alkylamines instead of NH_3 gave the N-alkylated derivatives (95JOC2251) (Scheme 67a).

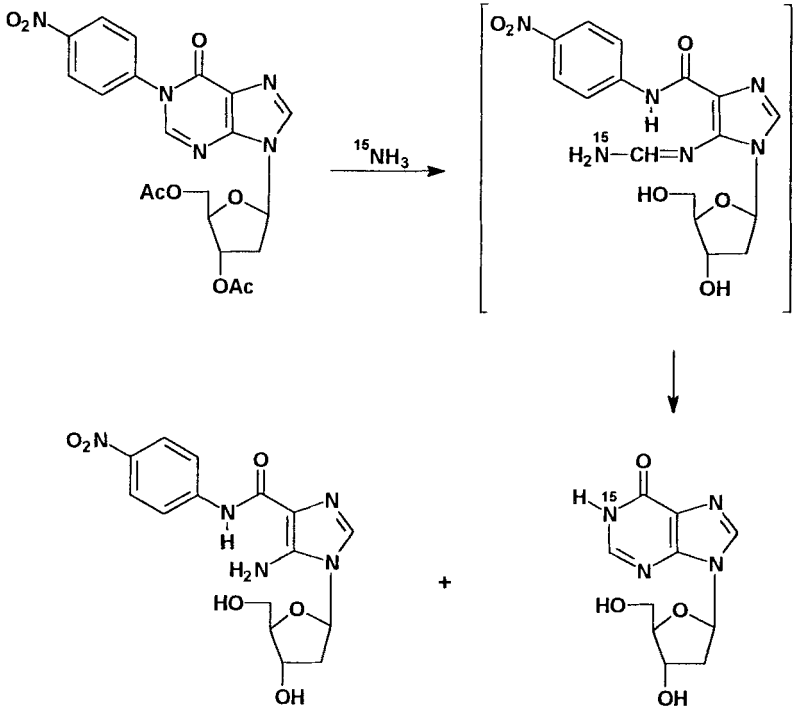
Rearrangement of 1-methyladenosine **211** to 6-methylaminopurine ribonucleoside **212** proceeded at room temperature at a rate proportional to the hydroxide ion concentration. Reduction of **211** by sodium borohydride gave 1-methyl-6-hydroadenosine **213,** which could be oxidized by air in al-



SCHEME 66



SCHEME 67



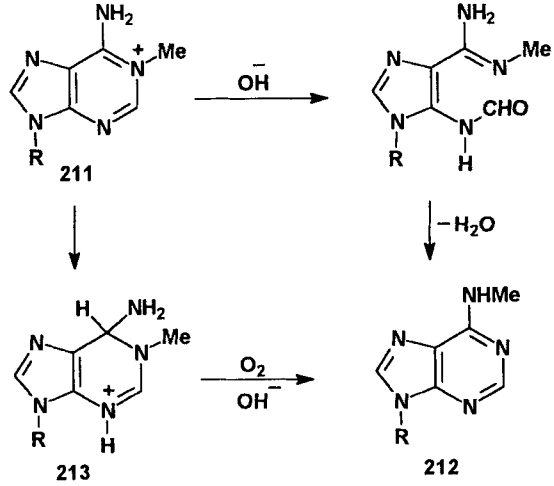
SCHEME 67A

kaline solution to give **212.** The reaction proceeded through ring opening (68B3453; 91MI2).

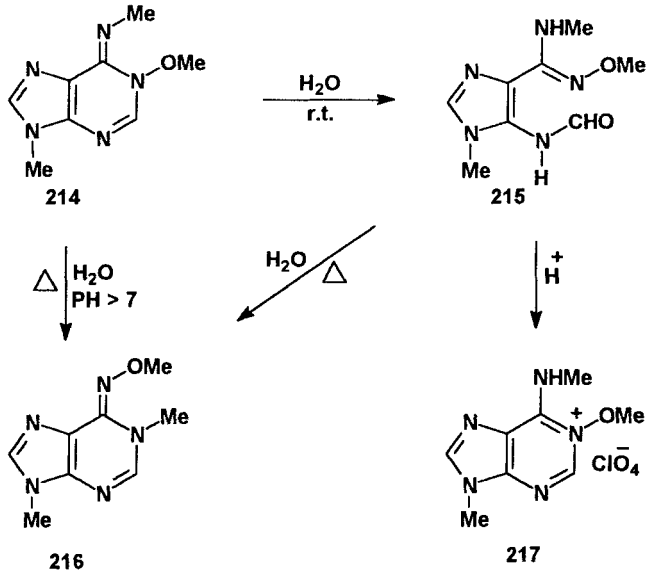
Kinetic analysis of the rearrangement of 1-methyladenosine to 6-*N*-methyladenosine in milk under temperature–time conditions of sterilization was found to be a first-order reaction (95MI1) (Scheme 68).

Treatment of 1-methoxy-9-dimethyladenine **214** with boiling H_2O under mildly alkaline condition afforded the rearranged product **216** (74CPB2211; 87CPB4482), whereas H_2O at room temperature gave the monocyclic compound **215** as an intermediate, which, when boiled in H_2O, afforded the rearranged product **216;** reversion to **214** appeared to occur to a negligibly small extent. When **216** was treated under similar conditions it gave neither intermediate **215** nor compound **214,** indicating that the equilibrium **214** ⇌ **215** ⇌ **216** in neutral or mildly alkaline solution favored the isomer with more electron-withdrawing groups attached to the exocyclic nitrogen atom. Under acid conditions, intermediate **215** recyclized at room temperature to both **216** and the 1-methoxy derivative **217** (71T2415). Rearrangement of adenosine analogs was also reported (75CPB2643; 90CPB652, 90CPB1392, 90CPB1536) (Scheme 69).

Reaction of 1-methoxyadenine (**218;** R=Me) with boiling water for 4 h furnished *N* -methoxyadenine **222,** while 1-benzyloxyadenine (**218;** R=Bn) in boiling DMAC gave the ring-opened derivative **219,** which underwent ring closure to give the rearranged product **221** and adenine 1-oxide **220** (71CPB1731).



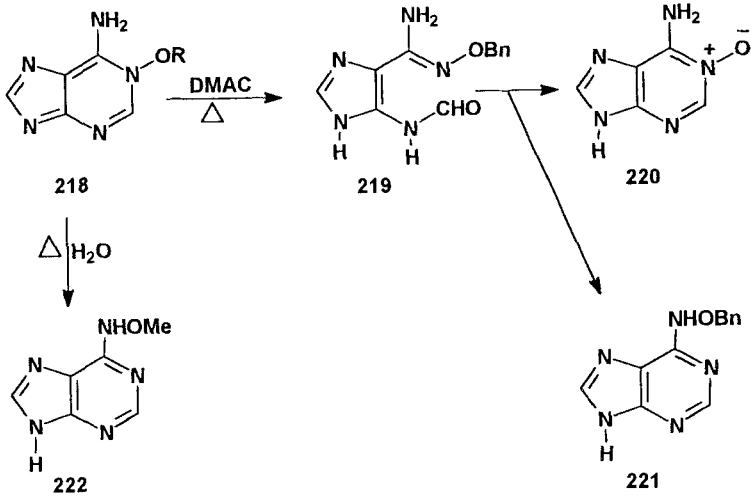
SCHEME 68



SCHEME 69

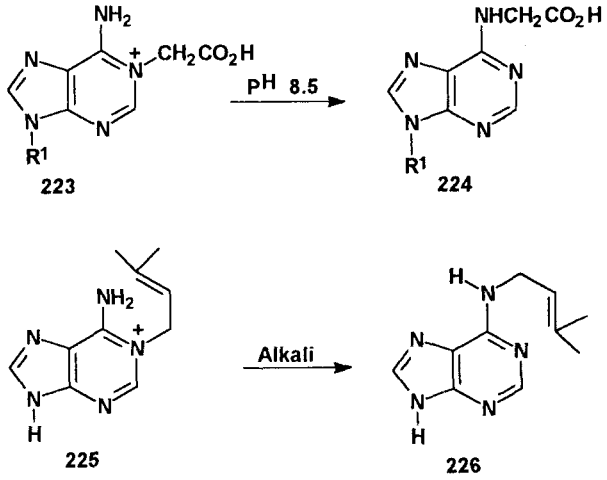
1-Methoxy-9-substituted adenine-2-*d*-hydroiodide and 1-methoxyadenosine 2-*d*-hydroiodide underwent rearrangement by the action of amberlite resin, Et_3N, or H_2O to give the 6-*N*-methoxy-9-substituted adenine-2-*d*. At pH 7.6, 1,9-dimethyladenine rearranged more rapidly than 1-methoxy-9-methyladenine, although the latter underwent ring opening 30 times as fast as the former (72T535; 75CPB54; 90H1593; 91CPB301) (Scheme 70).

The 1-*N*-carboxymethyl derivative **223** can be rearranged to the 6-N-carboxymethyl derivative **224** at pH 8.5. The 6-N-carboxymethylation of **223** directly took place in contrast with the NAD^+ derivatives, which must be first converted into NADH before undergoing rearrangement (86BBA64). When β-propiolactone reacted with single-stranded DNA at pH 11.7, 1-(2-carboxyethyl)adenine was completely rearranged by Dimroth rearrangement to 6-*N*-(2-carboxyethyl)adenine in DNA, whereas no conversion occurred at pH 7.5. The extent of the rearrangement was determined for 1-methyladenine, 1-(2-carboxyethyl)deoxyadenosine 5′-monophosphonic acid, and 5′-*O*-(2-carboxyethyl)phosphono-1-(2-carboxyethyl)deoxyadenosine (79MI1). 1,3-Di-(2-hydroxyethyl)adenosine 3′,5′-cyclic phosphate in 1 *M* NaOH failed to undergo rearrangement (86MI1). Rearrangement of the conjugate base **225** gave 6-*N*-(3-methylbut-2-enyl)adenine **226** by the action of alkali (64PNA73) (Scheme 71).



SCHEME 70

The 1-benzyl(methyl)-9-methyl-8-oxoadenine **227** underwent Dimroth rearrangement when it was treated with sodium hydroxide to give the 6-*N*-benzyl(methyl)-9-methyl-8-oxoadenine **228** (88H1145; 91TL97). Similarly, 1-methyl-8-oxoadenosine gave the 6-*N*-methyl-8-oxoadenosine (93CPB1850). The 8-bromo derivative **229** gave **231** (R=Br) (88H1145) through a nonisolable intermediate. The relative ease of rearrangement was



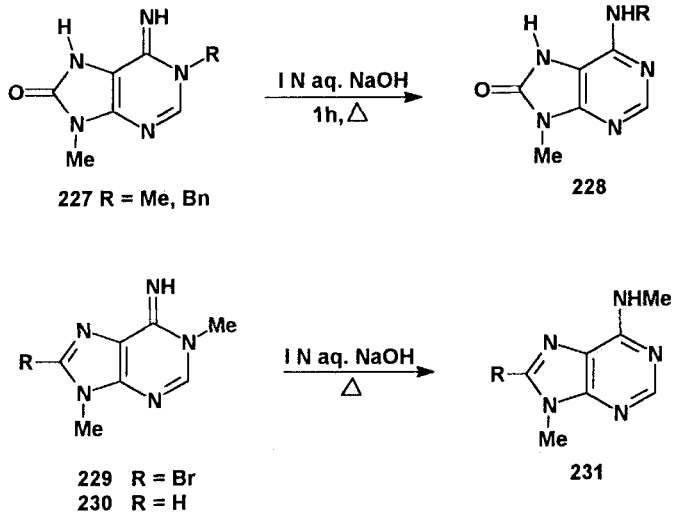
SCHEME 71

in the order **229** < **230** > **227.** The rate enhancement by the 8-bromo group was due to its electron-withdrawing effect on the 2-position where hydroxide ion attack occurred. Rate retardation by the 8-oxo group may be attributed to its electron-donating resonance effect (+R effect) on the 2-position (90CPB2591) (Scheme 72).

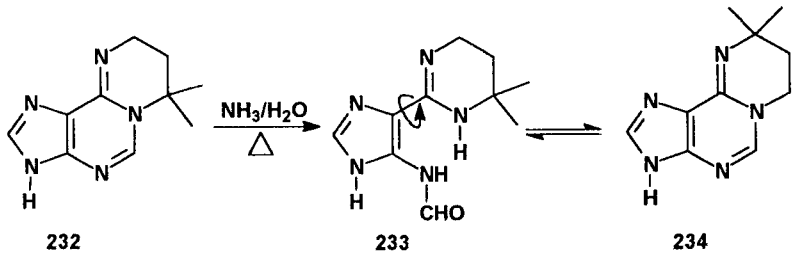
Rearrangement of 3,7,8,9-tetrahydro-7,7-dimethylpyrimido[2,1-*i*]purine **232** in 2 *N* aqueous ammonia at 110°C for 10 h, gave the 9,9-dimethyl tricyclic base **234** after the imidazole ring in **233** rotated 180° and the ring closed [68JCS(C)1731]. When a solution of the tricyclic base **232** in 1 *N* aqueous potassium hydroxide was set aside at 20°C, **233** and **234** formed slowly. However, when a solution of **232** in 2 N aqueous ammonia was heated at 85°C for 36 h, isomerization to **234** occurred to the extent of 60%, and very little of the imidazole derivative **233** was obtained. Thus, if an equilibrium (65JCS1165) exists between **232** and **234,** it should greatly favor the latter compound (Scheme 73).

1-*N*, 2-Polymethylene-bridged adenosine **235** on treatment with alkali underwent rearrangement to give the isomeric polymethylene-bridged adenosine **236** (79LA1872). Rearrangement of **237,** which has a carbon on C6, gave the deazapurine nucleoside **238** (81H1049) (Scheme 74).

h. *Thiazolopyrimidine.* Dimroth rearrangement of iminothiazolopyrimidine **239a** gave the aminothiazolopyrimidine **239b** (78JIC1040) (Scheme 75).

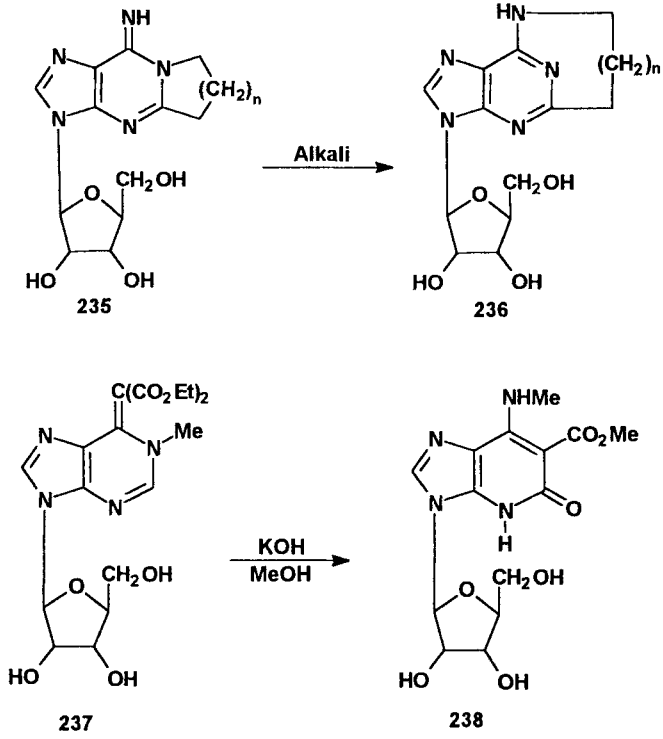


SCHEME 72

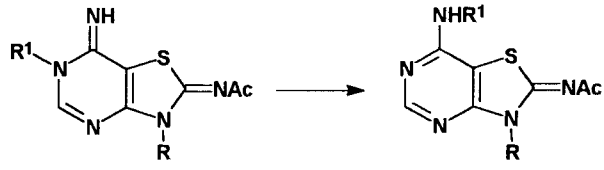


SCHEME 73

i. *Triazolopyrimidine.* Dimroth rearrangement of 1,2,3-triazolo[4,5-*d*]pyrimidine **240** to **242** was found to be greatly facilitated by the use of methylamine salts [73JCS(P1)2659]. The first step is a rapid addition of methylamine across the 2- and 3-positions of **240** to give **241a** and the 1–2 bond is opened by hydrolysis to produce the carbinol amine **241b,** which fi-



SCHEME 74



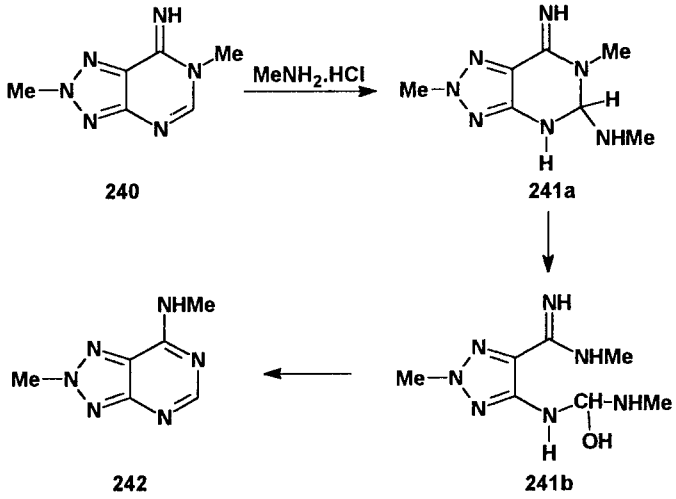
SCHEME 75

nally closed after rotation to give 8-methyl-6-methylamino-8-azapurine (**242**) (Scheme 76).

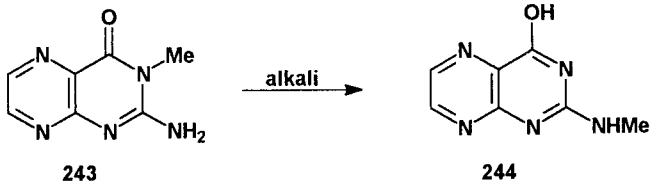
j. *Pteridines.* 2-Amino-3,4-dihydro-3-methyl-4-oxopteridine (**243**) rearranged in alkali to 4-hydroxy-2-methylaminopteridine (**244**) (60CB2015, 60TL17); the rate was studied (68MI1) (Scheme 77).

5. *Oxazines*

Rearrangement of this heterocyclic ring usually is accompanied by further reaction such as hydrolysis or dehydration. Thus, isomerization of iminoxazine **245** was followed by hydrolysis of the chlorine atom to give **246** (65M1352). On the other hand, 1,3-oxazine **247** isomerized in alkali to give **248** after dehydration (54JCS839) (Scheme 78).



SCHEME 76



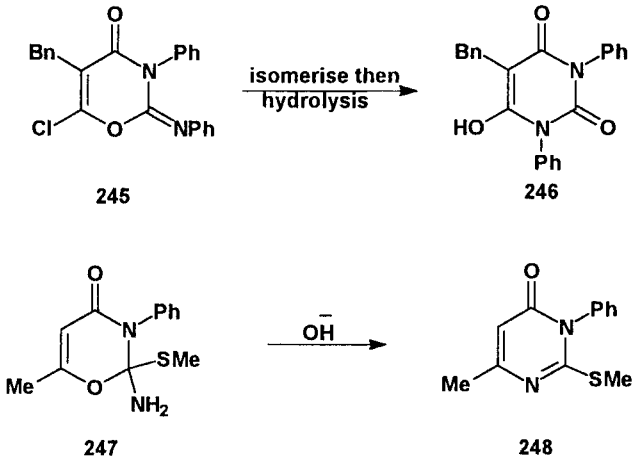
243 **244**

SCHEME 77

Reaction of the 2,3-dioxo-2,3-dihydro-4*H*-1,4-oxazines with dimethylsulfoxonium methylide introduced an exomethylene group with concomitant ring contraction to give the respective 4,5-dioxo-2,3,4,5-tetrahydrooxazole (94CPB739) (Scheme 78A) where an endocyclic carbon atom became exocyclic.

6. *Thiazines*

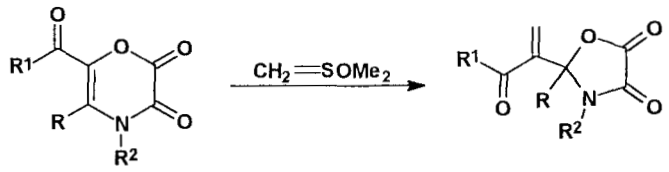
1-(4-Substituted phenyl)-6-phenyl-5,6-dihydro-2-thiouracils (**250**) can be obtained by the rearrangement of 2-(4-substituted phenylimino)-6-phenyl-5,6-dihydro-1,3-thiazin-4(3*H*)-one (**249**). The rearrangement proceeded in the aprotic solvent DMF in the presence of lithium hydride; the carbanion originating at the α-carbon facilitated C–S bond cleavage in the thiazine ring to yield the ambident ion, which in turn cyclized to the 2-thiouracil derivative **250** (87CCC2260).



245 **246**

247 **248**

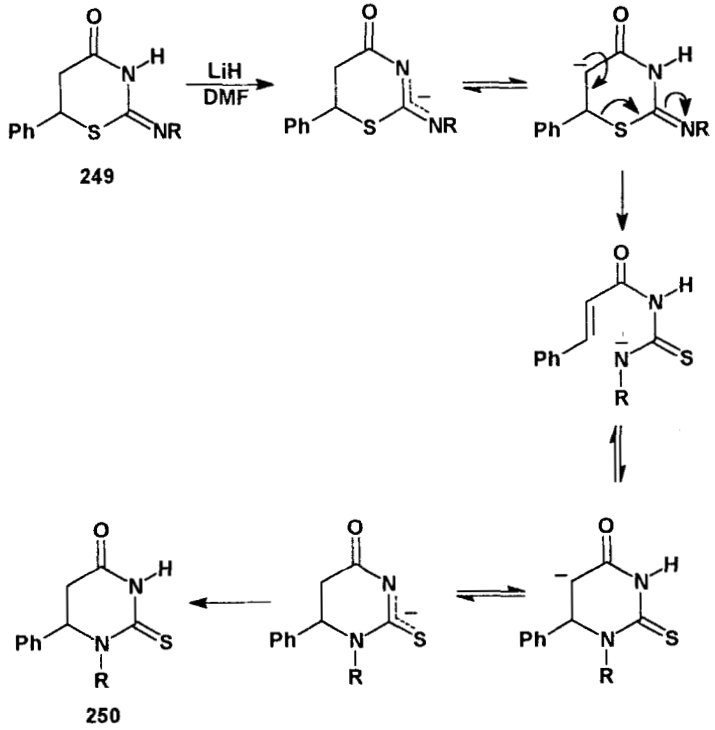
SCHEME 78



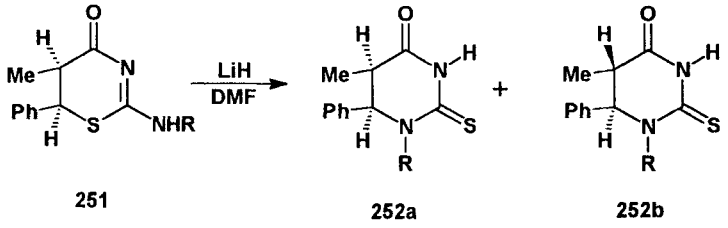
SCHEME 78A

Cis-2-(4-substituted phenyl)amino-5-methyl-6-phenyl-5,6-dihydro-1,3-thiazin-4-one (**251**) rearranged in the presence of lithium hydride in DMF, or in the presence of triethylamine in absolute ethanol to give *cis*- and *trans*-5-methyl-6-phenyl-1-(4-substituted phenyl)-5,6-dihydro-2-thiouracils (**252a** and **252b**) (91CCC1287) (Schemes 79 and 80).

The rearrangement of **253** gave pyrimidinethione **254** (90AQ62). Iminothiazine perchlorates **255** gave thioxopyrimidine **256** in the presence of base (88PS55).



SCHEME 79



251 **252a** **252b**

SCHEME 80

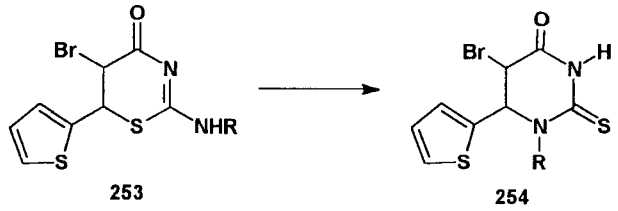
The pyrimidinethione **259** was prepared by rearrangement of 2-(methylamino) and 2-amino-4,6,6-trimethyl-6*H*-1,3-thiazine (**257**) and the 2-(phenylimino)thiazine **258** (75M1469) (Schemes 81, 82, and 83).

Reaction of ketene dithioacetals **260** with thioamides gave 5-substituted 2-methyl(phenyl)-6-methylthio-4-thioxopyrimidine (**262**) (92H1573). The reaction mechanism involves the addition of the thioamide to the ketene dithioacetal **260** to afford 2-cyano-3-methylthio-3-thioamido-propenonitrile or -propenoate intermediate, which cyclizes *in situ* by site-selective nucleophilic attack of the sulfur on the cyano group to give 6-imino-1,3-thiazine **261,** which rearranged to **262** (Scheme 84).

7. *Fused Thiazines*

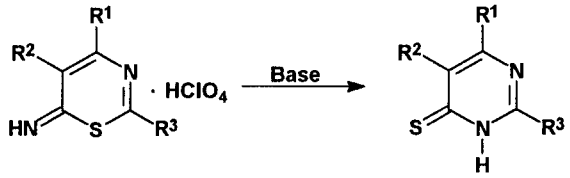
2-Amino-1,3-benzothiazin-4-ones (**263**) underwent rearrangement to give the quinazolinone-2-thione **264** (90AP857). The action of ethoxide base on anilinothienothiazines **265** gave the thioxopyrimidinone **266** (87S466), and the pyrazolothiazine **267** gave **268** (79KGS1687) (Schemes 85, 86, and 87).

Rearrangement of 2-imino-4-oxodihydro-5,6-benzo-1,3-thiazines **269** and **271** took place on heating above the melting point to give **270** and **273,** respectively. In case of **269,** the direction of rearrangement depended on the electron density on the nitrogen atoms. In the case of **271, 273** is more stable than **272** (67ZC231) (Scheme 88).

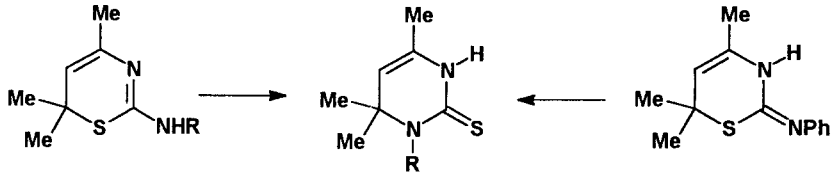


253 **254**

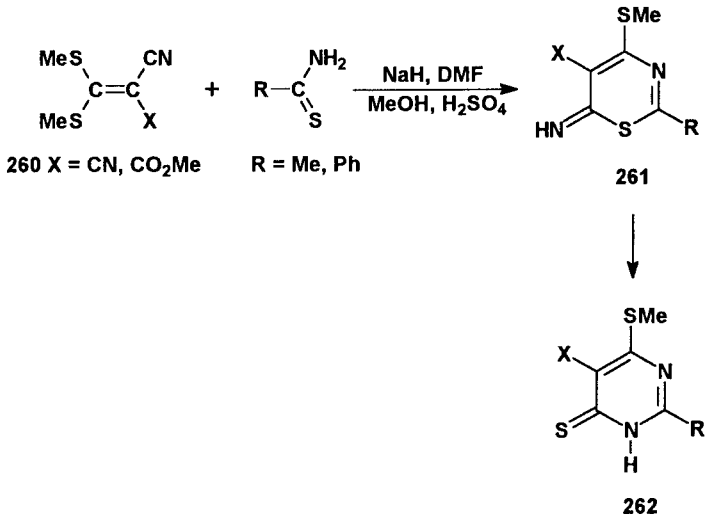
SCHEME 81



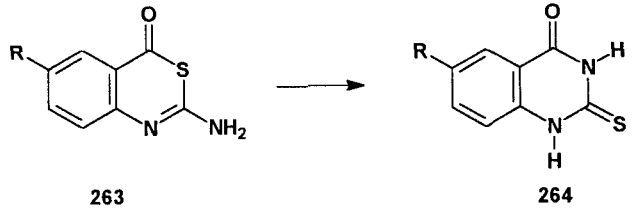
SCHEME 82



SCHEME 83

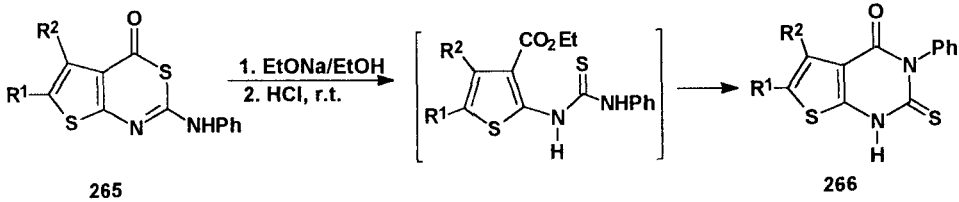


SCHEME 84



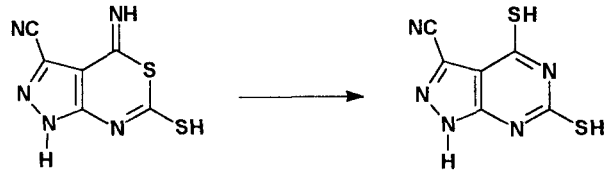
263 264

SCHEME 85



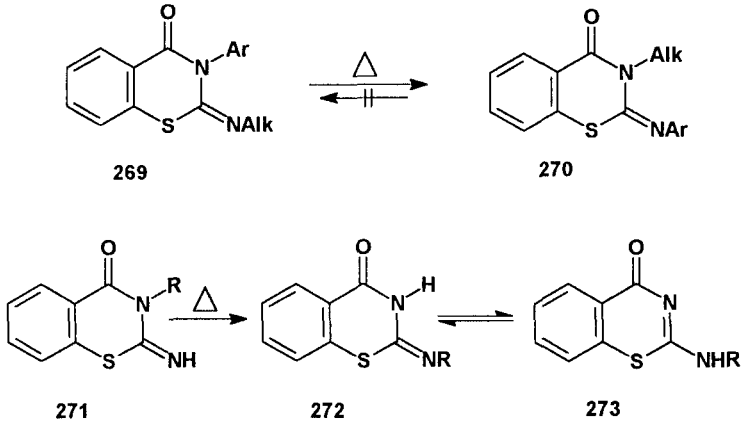
265 266

SCHEME 86



267 268

SCHEME 87



269 270 271 272 273

SCHEME 88

8. *Pyrazines*

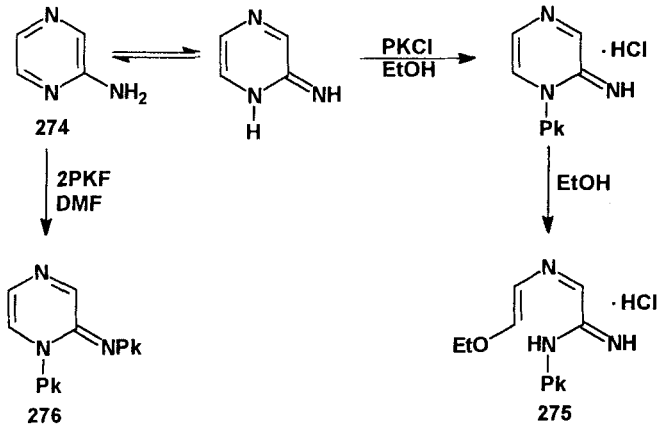
2-Aminopyrazine (**274**) unlike 2-aminopyridine and 2-aminopyrimidine, failed to react with picryl chloride (PKCl) to give 2-picrylaminopyrazine. When equimolar quantities of **274** and PKCl were dissolved in absolute ethanol at 25°C, the hydrochloride of 1-ethoxy-5-imino-5-picrylamino-3-aza-1,3-pentadiene (**275**) was formed and this failed to give the 2-picrylaminopyrazine when treated with an equivalent amount of base. However, treatment of **274** with 2 molar equivalents of picryl fluoride (PKF) in DMF produced 1-picryl-2-picrylimino-1,2-dihydropyrazine (**276**) (73JHC275) (Scheme 89).

C. Heterocycles with Three Heteroatoms in the Ring

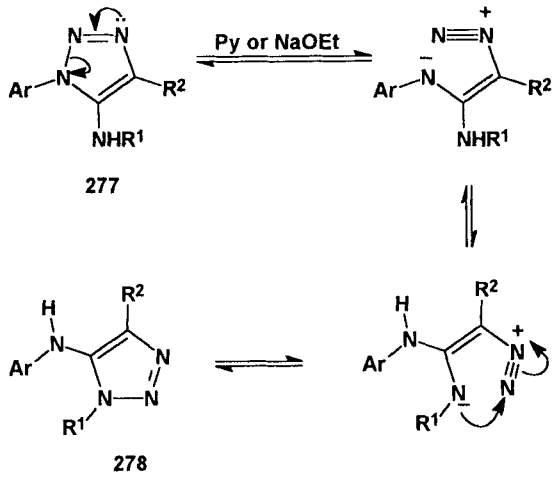
1. *Triazoles*

The aminotriazoles **277** rearranged in pyridine or alcoholic sodium ethoxide to give the anilinotriazoles **278** [70JCS(C)230; 73LA578; 80JCR(S)308; 88S851; 91HCA899]. The reaction was also successful with the 4-pyridyl (89BSB343) and 4-thiadiazolyl derivatives (92CPB357).

Heating 4-substituted 5-amino-1-phenyl-1,2,3-triazole (**277**) in acetic anhydride afforded the acetyl derivative of the isomeric 4-substituted 5-anilino-1,2,3-triazole (**278**). However, the anilino isomers and their acetyl derivatives retrogress to the acetyl derivatives of the amino compounds on prolonged heating in acetic anhydride [71JCS(C)706] (Scheme 90).

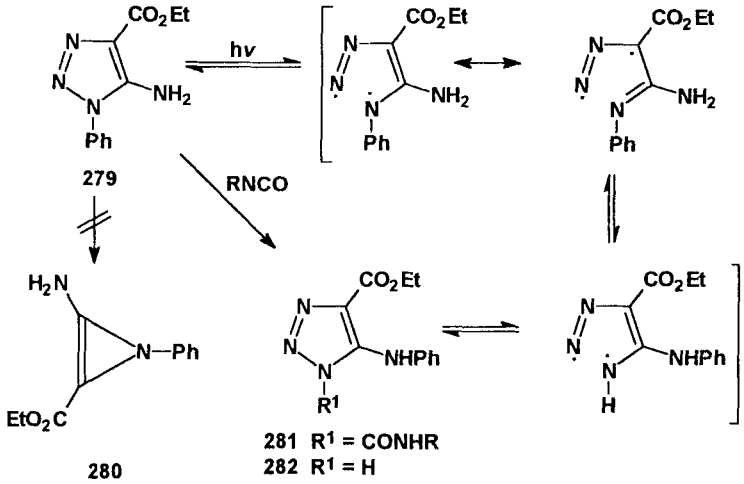


Scheme 89



SCHEME 90

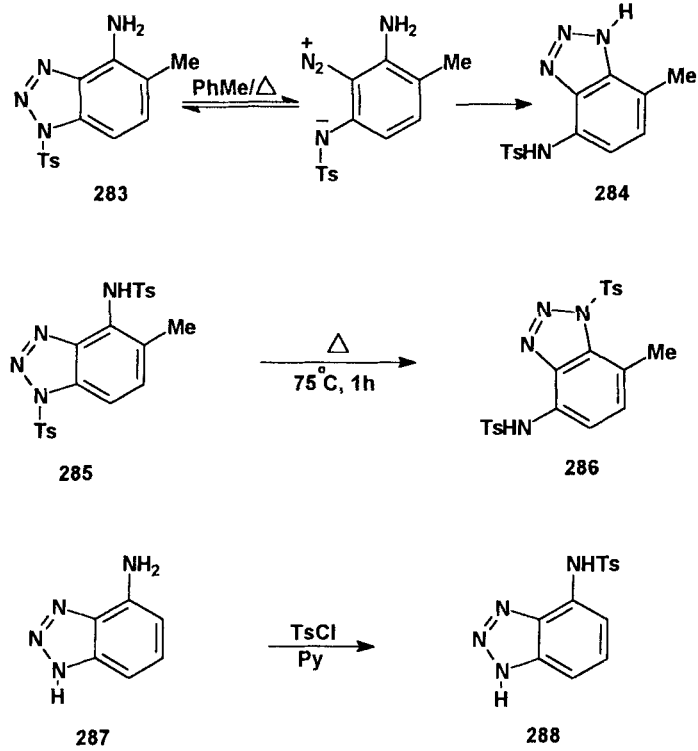
Rearrangement of **279** took place on the addition of alkylisocyanates to give **281** (89CZ11). 5-Amino-4-ethoxycarbonyl-1-phenyl-1,2,3-triazole (**279**) under UV irradiation gave the rearranged product **282** and not the ketene imine **280,** which can be formed from some 1,2,3-triazoles on similar treatment. This is an example of photochemical Dimroth rearrangement (02CB4041; 57JOC654; 76ACH265; 77BCJ2505). The reaction was also effected thermally in H_2O, Me_2SO, Ac_2O, or in alkaline solution (09LA183; 83YZ594) (Scheme 91).



SCHEME 91

When 4-amino-5-methyl-1-(*p*-toluenesulfonyl)benzotriazole (**283**) was boiled in toluene for 3 h, rearrangement into 7-methyl-4-[(*p*-toluenesulfonyl)amino]benzotriazole (**284**) was complete. However, the same compound was boiled in benzene for 1.5 h and produced a trace of **284.** The bistosylate **285** was stable in nonpolar solvents and its rearrangement to **286** was accelerated on raising the temperature. No rearrangement of **285** to **286** was observed in chloroform and it was slow in toluene. No rearrangement from **286** to **285** was observed in DMSO-d_6 at room temperature (92JOC190). Furthermore, when 4-aminobenzotriazole **287** was treated with one equivalent of *p*-toluenesulfonyl chloride in pyridine, 4-[(*p*-toluenesulfonyl)amino]benzotriazole (**288**) was obtained either by the rearrangement of the 1-sulfonyl–substituted compound or by its direct formation. Compound **288** was stable when heated in toluene for 5 h (Scheme 92).

5-Chloro-1-phenyl-1,2,3-triazole (**289;** X=CH) when heated with 5 equivalents of hydrazine hydrate in methanol yielded the rearranged tria-



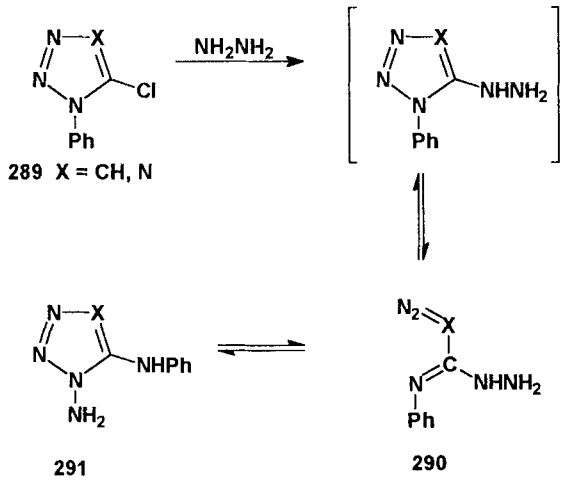
SCHEME 92

zole **291** (X=CH) through the rearrangement of 5-hydrazino intermediates. The reaction involves the exchange of an endocyclic nitrogen atom with an exocyclic one and proceeds via the diazoamidine intermediate **290** (X=CH) (88BSB543; 89BSB343). The structure of **291** was established by comparing its ^{13}C NMR spectra with that of **289.** The ipso-aryl C-atom of **291** is deshielded and the *ortho-* and *para*-C-atoms are shielded relative to those of **289** (89BSB343) (Scheme 93).

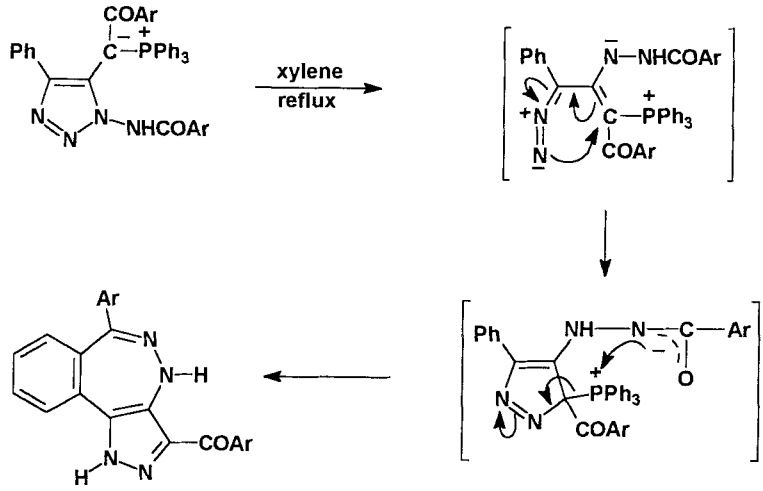
When the 1-aroyamino-4-phenyl-1,2,3-triazol-5-yl-aroylmethylphosphorus ylide was boiled under reflux in xylene or chlorobenzene, it rearranged to the pyrazolo[4,3-*d*][2,3]benzodiazepines (95TL5637) (Scheme 93a). The mechanism involved a ring opening of the triazole and a recyclization to a pyrazole (Scheme 93A).

2. *Thiadiazoles*

5-Hydrazino-1,2,3-thiadiazole **295** was formed when **293** was allowed to react with 2 equivalents of hydrazine hydrate in ethanol at room temperature, but with an excess of hydrazine the rearranged salt **296** was isolated. However, on acidification with hydrochloric acid **296** yielded **295,** indicating the reversibility of the rearrangement (89JHC1811). When **296** was treated with benzaldehyde at room temperature, the rearranged product **297** was formed, while methylation of **296** and reaction of the resulting **298** with benzaldehyde yielded **299.** The rearrangement proceeded through



SCHEME 93



SCHEME 93A

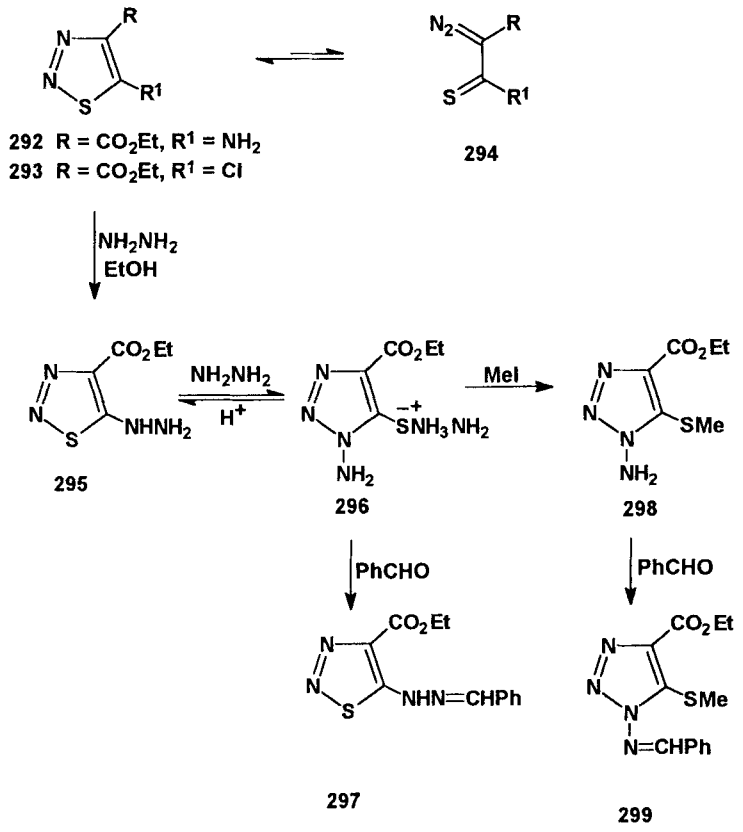
electrocyclic ring opening of **292** or **293,** followed by ring closure of the intermediate **294** involving the substituent at the 4- or 5-positions.

Compound **295** exhibits a small upfield shift for C4 (4 ppm) and a downfield shift for C5 (5 ppm) compared with those in **292.** Compound **297** has similar absorption for the ring carbon atoms and also exhibits a diagnostic hydrazone C=N resonance at 147.7 ppm. The hydrazone C=N signal of **299** is shifted downfield by 10 ppm (Scheme 94).

5-Arylamino-4-acyl-1,2,3-thiadiazole (**300**) underwent rearrangement when heated in piperidine to give after acidification 5-mercapto-1-aryl-4-acyl-1,2,3-triazole (**301**) (69CB417; 76MI1). The rearrangement of 1,3,4-thiadi azoline **302** gave 1,2,4-triazole **303** on heating in alcohols (75M1291) (Schemes 95 and 96).

Rearrangement of 3-amino-5-thiomethyl-1,2,4-thiadiazoles was detected in the mass spectra of these compounds labeled with ^{15}N in the 3-amino substituent or the ring 2-position (86MI4).

Treatment of 3-(2-pyridylimino)-3*H*-1,2,4-thiadiazolo[4,3-*a*]pyrimidine (**304;** R=2-pyridyl) with either 10% ethanolic HCl or NaOH resulted in the formation of 2-(2-pyridylimino)-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine (**305;** R=2-pyridyl), which was alternatively synthesized by the action of sulfuryl chloride on thiourea **306** (74JOC3783). Under similar conditions 5,7-dimethyl-3-(2,6-dimethyl-4-pyrimidylimino)-3*H*-1,2,4-thiadiazolo[4,3-*c*]pyrimidine (**307**) gave no rearranged products. Thus, it afforded **308** with HCl, whereas attempted rearrangement in NaOH gave a product which corre-

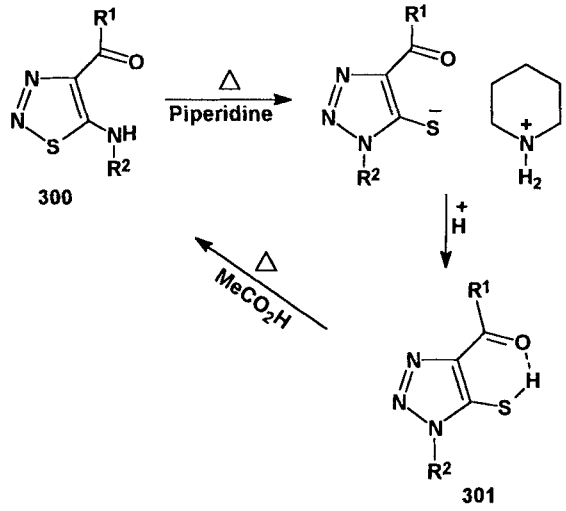


SCHEME 94

sponded to the addition of water to the starting material and formation of **309** as a Dimroth intermediate. Hydrolysis of **309** in HCl resulted in the formation of **308**. Heating **309** in $POCl_3$ resulted in the formation of 5,7-dimethyl-2-(2,6-dimethyl-4-pyrimidylimino)-2*H*-1,2,4-thiadiazolo[2,3-*c*]-pyrimidine (**310**), a resonance hybrid [**310** ↔ **311**] (Scheme 97).

3. *Dithiazoles*

Compounds of type **312** and **313** can undergo rearrangement under the influence of Lewis acids to give **315** and **316,** respectively, via betaines of type **314** for **315** (78JOC4951).

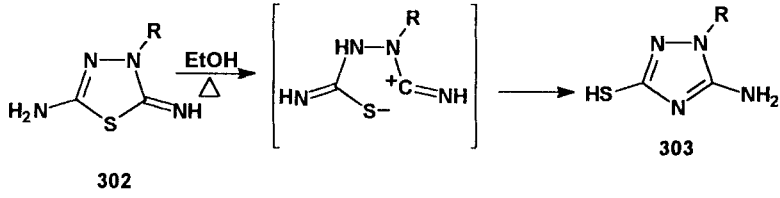


SCHEME 95

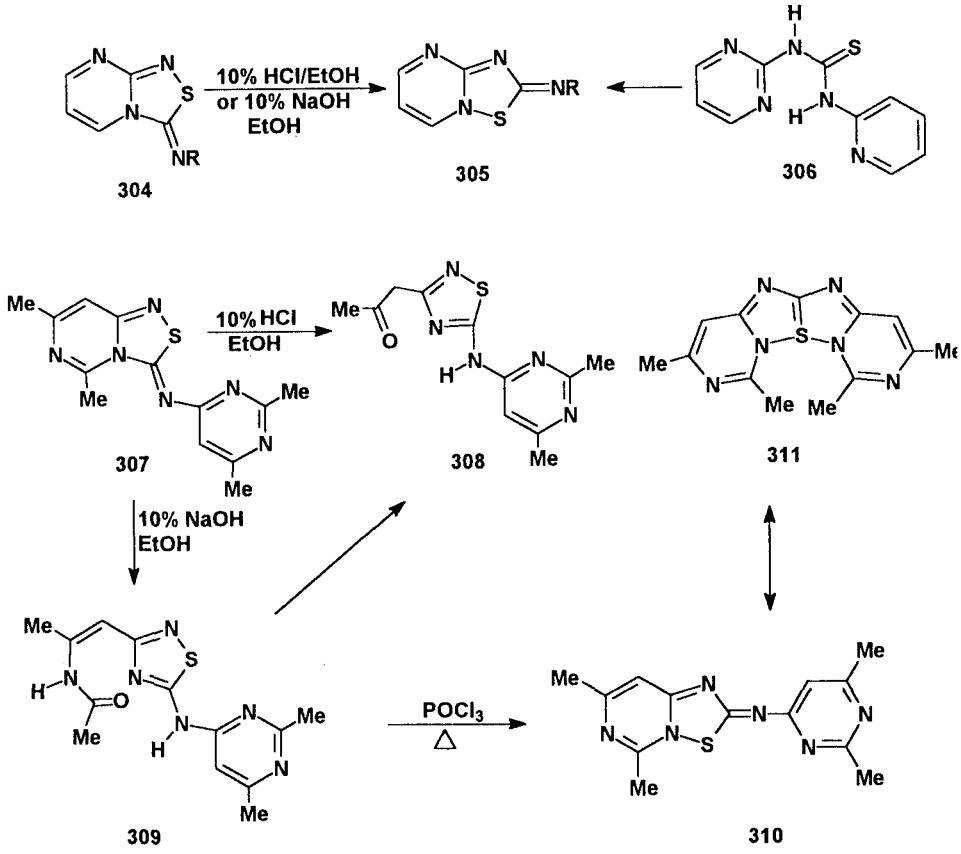
Disubstituted 5-imino-1,2,4-dithiazolidine-3-thiones (**317**) with a 5-alkylimino group rearranged when boiled in triethylamine in the presence of ethanol to give **318** (91JPR107) (Scheme 98).

4. *Triazines*

a. *1,2,3-Triazines.* 3-Substituted 3,4-dihydro-4-imino-1,2,3-benzotriazines (**319**) rearranged to the isomeric substituted 4-amino-1,2,3-benzothiazines (**320**) in acetic acid regardless of the nature of the 3-substituents [74JCS(P1)609]. A −I or −M type of substituent in the 3-aryl nucleus of the 4-iminotriazines **319** accelerates the rearrangement, especially when the substituents occupy an *ortho* or *para* position. For example, the



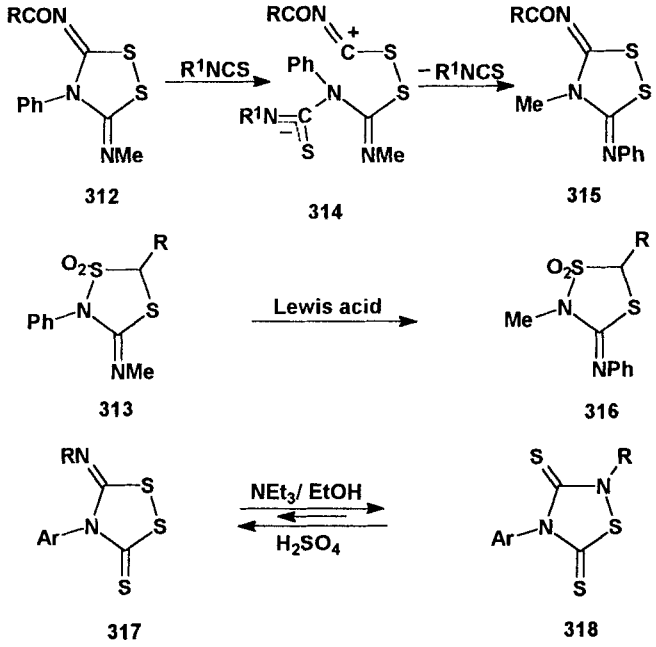
SCHEME 96



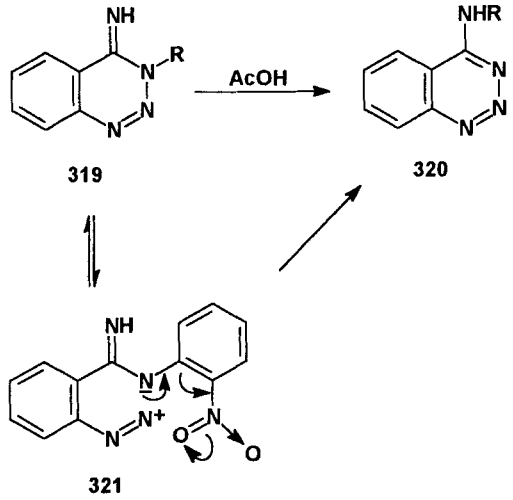
SCHEME 97

o-nitrophenyl derivative of the imine **319** was so unstable that it could not be isolated; it rearranged spontaneously to the isomer 4-*o*-nitroanilino-1,2,3-benzotriazine (**320**), due to the electronic influence of the *o*-nitro substituent in **321.** In contrast, +I substituents stabilized the 4-iminotriazines. 4-Aminobenzotriazines are stable in acetic acid (Scheme 99).

3-Ethoxycarbonylmethyl-4-arylazomethylene-3,4-dihydro-1,2,3-benzotriazine (**322**) rearranged to **325** when it was heated in ethanol [91JHC1709]. The reactivity of **322** suggested that the combined electron-withdrawing effect of the ethoxycarbonylmethyl group at N3 and the azomethylene group at C4 promoted the cleavage of the N2–N3 bond of



SCHEME 98

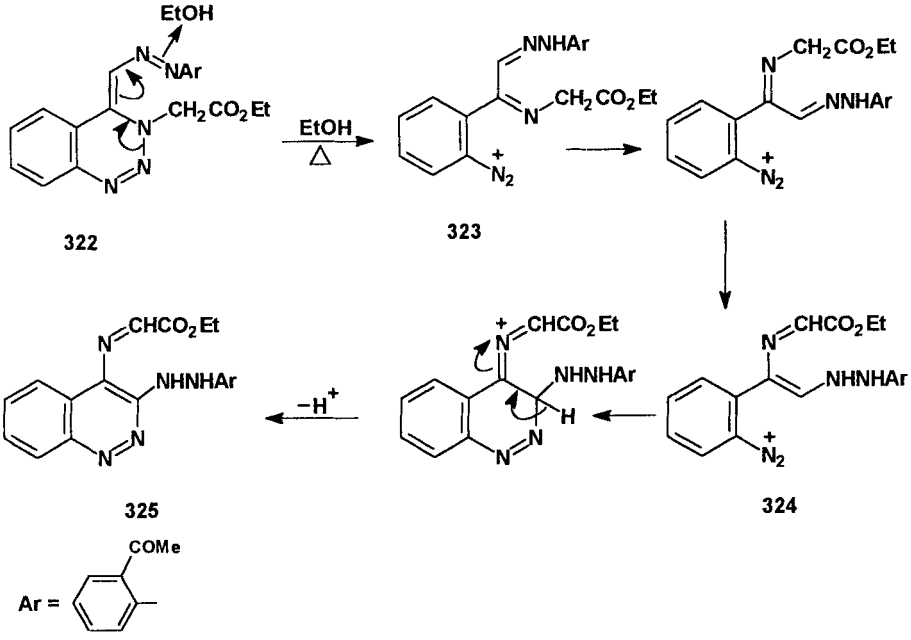


SCHEME 99

the triazine ring. Also, the protonation of the azo nitrogen by solvent facilitated the ring-opening step to give the diazonium intermediate **323.** Bond rotation and a 1,5-prototropic shift gave the isomeric diazonium cation **324,** which then underwent ring closure and loss of a proton to give the rearranged product **325** (Scheme 100).

b. *1,3,5-Triazines.* The rearrangement of 1-(nitrophenyl)-4,6-diamino-1,3,5-triazines **326** to their isomers **327** was best affected in boiled ethanolic pyridine (93JHC849). The rearrangement of compounds having an imino or azido group on the aryl ring proceeded in lower yields than those of the corresponding nitro analogs, where the electron-withdrawing nitro groups stabilized the transient dipolar acyclic species as intermediates. However, attempts to trap any intermediate failed.

Rearrangement of various acylamino-1,3,5-triazines, e.g., **328,** gave **329a** or **329b.** However, rearrangement was not observed for other substituents (85MI2; 86MI2, 86MI5; 87MI1, 87MI2). The rate of rearrangement in $EtOH/H_2O$ increased with increasing ionizing power of the solvent and proceeded by nucleophilic attack of H_2O. When 2,4-bis(2-hydroxy-1-

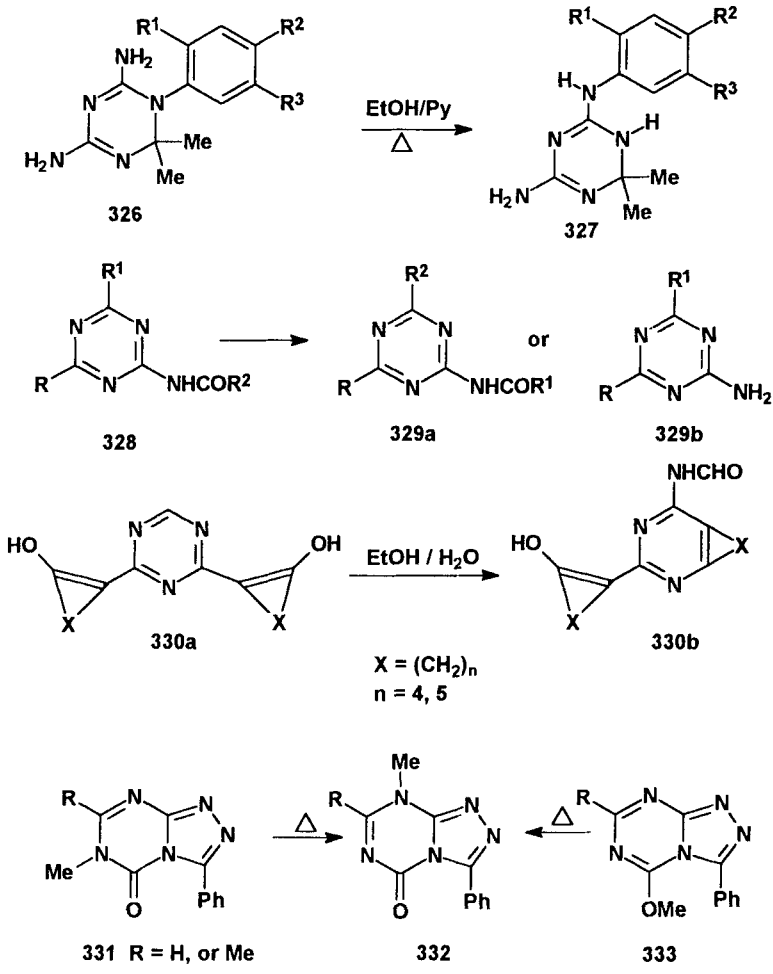


SCHEME 100

cycloalkenyl)-1,3,5-triazines (**330a**) were subjected to rearrangement in $EtOH/H_2O$, they were converted into (hydroxycycloalkenyl)formylaminopyrimidines **330b** (88MI1). Thermal rearrangement of **331** and **333** gave **332** (70T3357) (Scheme 101).

5. *Oxadiazines*

4-(Dialkylamino)-2*H*-1,3,5-oxadiazine-2-thiones (**334**) were very sensitive toward acids and rearranged completely to 4-(dialkylamino)-2*H*-1,3,5-



SCHEME 101

thiadiazin-2-ones (**335**) by treatment with acetic acid (89LA931) (Scheme 102).

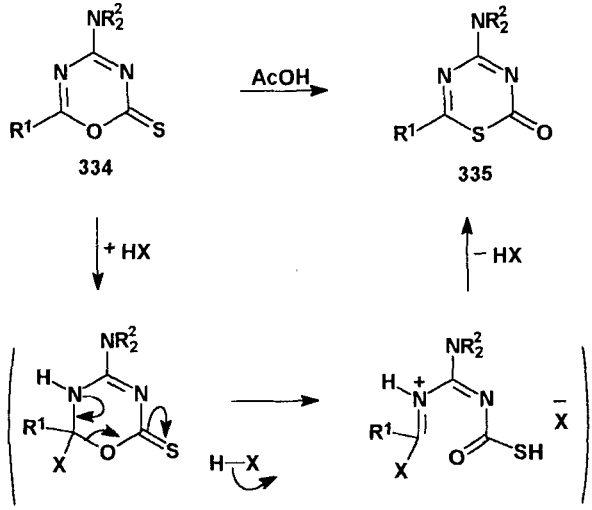
D. Heterocycles with Four Heteroatoms in the Ring

1. *Tetrazoles*

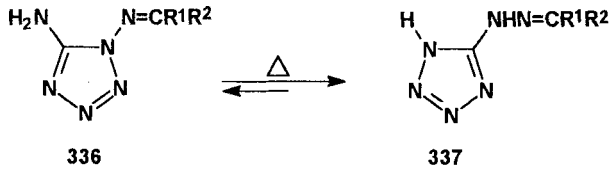
When 5-chloro-1-phenyltetrazole (**289**; X=N) was heated with five equivalents of hydrazine hydrate in methanol, it yielded the tetrazole **291** (X=N) through rearrangement of the 5-hydrazino intermediate (88BSB543; 89BSB343).

Heating imines **336** derived from 1,5-diaminotetrazole in DMSO provided hydrazones **337** via Dimroth rearrangement. The reaction was greatly favored due to the electron-withdrawing groups attached to the imine carbon atom (90CB1575) (Scheme 103).

An *ab initio* study of the Dimroth rearrangement of 5-amino-1,2,3,4-tetrazole (**338**) to **339** led to the conclusion that in the vapor phase the rate-determining step was not ring–chain isomerism, but was either the Z–E isomerism around the C=N double bond or the 1,3-sigmatropic shift of the proton (82JHC943) (Scheme 104).



Scheme 102

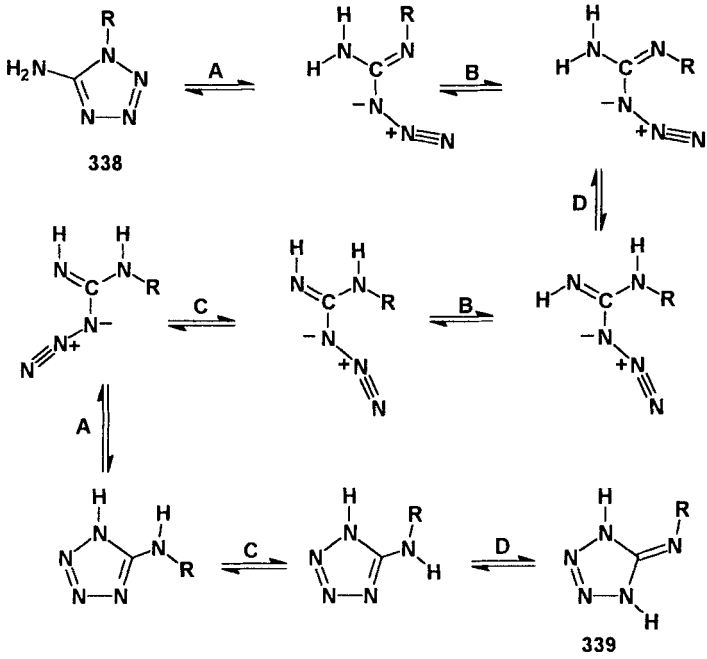


336 337

SCHEME 103

2. *Thiatriazolines*

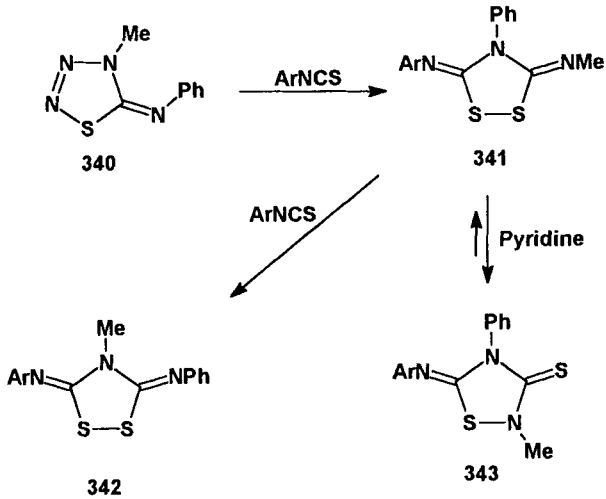
Reaction of 4-alkyl-5-arylimino-1,2,3,4-thiatriazoline (**340**) with *p*-nitrophenylisothiocyanate in pyridine yielded three products, **341, 342,** and **343.** Thus, **340** underwent cycloaddition to give the dithiazolidine



338 339

A Azido tetrazole isomerization
B Z/E isomerization around C=N double bond
C Cis/ trans isomerization around C-N single bond
D 1,3-Sigmatropic shift of the proton

SCHEME 104



SCHEME 105

341, which then gave **342.** The isomerization of **341** to **343** via Dimroth rearrangement was catalyzed by pyridine (89BSB879) (Scheme 105).

ACKNOWLEDGMENT

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REFERENCES

1888CB867 B. Rathke, *Ber. Dtsch. Chem. Ges.* **21,** 867 (1888).
02CB4041 O. Dimroth, *Ber. Dtsch. Chem. Ges.* **35,** 4041 (1902).
09LA183 O. Dimroth, *Justus Liebigs Ann. Chem.* **364,** 183 (1909).
21CB814 A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *Ber. Dtsch. Chem. Ges.* **54,** 814 (1921).
25CB393 F. Reindel and H. Rauch, *Ber. Dtsch. Chem. Ges.* **58,** 393 (1925).
28CB1223 A. E. Tschitschibabin and A. W. Kirssanow, *Ber.* **61,** 1223 (1928).
52BBA369 J. J. Fox and D. Shugar, *Biochim. Biophys. Acta* **9,** 369 (1952).
52DOK223 Ya. Gol'dfarb and Ya. Danyushevskii, *Dokl. Akad. Nauk SSSR* **87,** 223 (1952).
54JCS839 R. N. Lacey, *J. Chem. Soc.* 839 (1954).

55JCS1858 H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.*, 1858 (1955).

55JCS4035 D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 4035 (1955).

57JOC654 E. Lieber, T-S. Chao, and C. N. R. Rao, *J. Org. Chem.* **22,** 654 (1957).

58AG400 J. Goerdeler and W. Roth, *Angew. Chem.* **70,** 400 (1958).

58CB1395 K. Sirakawa, *Chem. Ber.* **78,** 1395 (1958).

59CB903 K. Sirakawa, *Chem. Ber.* **79,** 903 (1959).

59JA178 J. J. Fox, D. V. Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.* **81,** 178 (1959).

59JOC787 C. F. H. Allen, H. R. Beifuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Alan, *J. Org. Chem.* **24,** 787 (1959).

60CB2015 W. Pfleiderer, F. Liedek, R. Lohrmann, and M. Rukwied, *Chem. Ber.* **93,** 2015 (1960).

60JA222 C. D. Jardetzky and O. Jardetzky, *J. Am. Chem. Soc.* **82,** 222 (1960).

60JA3147 E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.* **82,** 3147 (1960).

60JCS1829 L. A. Williams, *J. Chem. Soc.*, 1829 (1960).

60TL17 D. J. Brown and N. W. Jacobsen, *Tetrahedron Lett.* **25,** 17 (1960).

61NAT(L)828 D. J. Brown, *Nature (London)* **189,** 828 (1961).

63BJ127 P. D. Lawley and P. Brookes, *Biochem. J.* **89,** 127 (1963).

63CB534 J. Goerdeler and W. Roth, *Chem. Ber.* **96,** 534 (1963).

63JCS1276 D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1276 (1963).

63JCS1284 D. D. Perrin, *J. Chem. Soc.*, 1284 (1963).

63JCS56412 G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 56412 (1963).

64PNA73 N. J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U.S.A.* **51,** 73 (1964).

65JA1980 E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.* **87,** 1980 (1965).

65JCS1165 D. J. Brown, B. T. England, and J. S. Harper, *J. Chem. Soc.*, 1165 (1965).

65JCS3357 G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 3357 (1965).

65JCS7071 D. D. Perrin and I. H. Pitman, *J. Chem. Soc.*, 7071 (1965).

65JOC2766 T. J. Delia, M. J. Olsen, and G. B. Brown, *J. Org. Chem.* **30,** 2766 (1965).

65M1352 G. Kleineberg and E. Ziegler, *Monatsh. Chem.* **96,** 1352 (1965).

66CB2237 A. Kreutzberger, *Chem. Ber.* **99,** 2237 (1966).

66CI(L)1967 T. Fujii, T. Itaya, C. C. Wu, and S. Yamada, *Chem. Ind. (London)*, 1967 (1966).

66JCS(C)164 D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc. C*, 164 (1966).

66JCS2038 S. E. Mallett and F. L. Rose, *J. Chem. Soc.*, 2038 (1966).

66JOC265 K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.* **31,** 265 (1966).

66ZC181 M. Wahren, *Z. Chem.* **6,** 181 (1966).

67B3625 W. A. H. Grimm and N. J. Leonard, *Biochemistry* **6,** 3625 (1967).

67JCS(C)903 D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc. C*, 903 (1967).

67JCS(C)1856 D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc. C*, 1856 (1967).

67JCS(C)1928 D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc. C*, 1928 (1967).

67JOC1151 J. C. Parham, J. Fissekis, and G. B. Brown, *J. Org. Chem.* **32,** 1151 (1967).

67ZC231 G. Wagner and P. Richter, *Z. Chem.* **7,** 231 (1967).

68AJC2813 D. J. Brown and B. T. England, *Aust. J. Chem.* **21,** 2813 (1968).

68B3453 B. Macon and R. Wolfenden, *Biochemistry* **7,** 3453 (1968).

68JCS(C)1452 D. J. Brown, P. W. Ford, and M. N. Paddon-Row, *J. Chem. Soc. C,* 1452 (1968).

68JCS(C)1731 D. M. G. Martin and C. B. Reese, *J. Chem. Soc. C,* 1731 (1968).

68JCS(C)2026 P. Brookes, A. Dipple, and P. D. Lawley, *J. Chem. Soc. C,* 2026 (1968).

68JHC485 K. T. Potts and S. W. Schneller, *J. Heterocycl. Chem.* **5,** 485 (1968).

68MI1 D. J. Brown, Mech. Mol. Migr. **1,** 209 (1968).

69BSF2492 J. Daunis, R. Jacquier, and P. Viallefont, *Bull. Soc. Chim. Fr.,* 2492 (1969).

69BSF3670 J. Daunis, R. Jacquier, and P. Viallefont, *Bull.* Soc. *Chim. Fr.,* 3670 (1969).

69CB417 M. Regitz and H. Scherer, *Chem. Ber.* **102,** 417 (1969).

69CPB1128 A. Yamazaki, I. Kumashiro, and T. Takenishi, *Chem. Pharm. Bull.* **17,** 1128 (1969).

69JCS(CC)458 J. A. Montgomery and H. J. Thomas, *J. Chem. Soc., Chem. Commun.,* 458 (1969).

69ZC241 M. Wahren, *Z. Chem.* **9,** 241 (1969).

70JCS(C)230 A. Albert, *J. Chem. Soc. C,* 230 (1970).

70JCS(CC)1524 F. L. Rose, G. J. Stacey, P. J. Taylor, and T. W. Thompson, *J. Chem. Soc., Chem. Commun.,* 1524 (1970).

70JHC1019 K. T. Potts and C. R. Surapaneni, *J. Heterocycl. Chem.* **7,** 1019 (1970).

70JOC3448 K. T. Potts and E. G. Brugel, *J. Org. Chem.* **35**(10), 3448 (1970).

70JPR254 M. Muehlstaedt, H. Krausmann, and G. Fischer, *J. Prakt. Chem.* **312,** 254 (1970).

70T3357 J. Kobe, B. Stanovnik, and M. Tisler, *Tetrahedron* **26,** 3357 (1970).

71CB2702 H. Reimlinger, R. Jacquier, and J. Daunis, *Chem. Ber.* **104,** 2702 (1971).

71CPB1731 T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.* **19,** 1731 (1971).

71JCS(C)250 D. J. Brown and B. T. England, *J. Chem. Soc. C,* 250 (1971).

71JCS(C)706 G. Tennant and D. R. Sutherland, *J. Chem. Soc. C,* 706 (1971).

71JCS(C)2507 D. J. Brown and B. T. England, *J. Chem. Soc. C,* 2507 (1971).

71JHC643 P. Guerret, R. Jacquier, and G. Maury, *J. Heterocycl. Chem.* **8,** 643 (1971).

71MI1 G. L'Abbé, *Ind. Chim. Belge* **36,** 3 (1971) [*CA* **74,** 99917 (1971)].

71T2415 T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *Tetrahedron* **27,** 2415 (1971).

72JA(82)4708 R. P. Panzica, R. J. Rousseau, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.* **82,** 4708 (1972).

72JA(94)8542 E. R. Garrett and P. J. Mehta, *J. Am. Chem. Soc.* **94,** 8542 (1972).

72JCS(CC)52 C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Chem. Soc., Chem. Commun.,* 52 (1972).

72JMC182 J. A. Montgomery, and W. J. Thomas, *J. Med. Chem.* **15,** 182 (1972).

72JOC3601 C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.* **37,** 3601 (1972).

72T535 T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron* **28,** 535 (1972).

73B2179 M. J. Robins and E. M. Trip, *Biochemistry* **12,** 2179 (1973).

73B4074 D. J. Brunswick and B. S. Cooperman, *Biochemistry* **12,** 4074 (1973).

73JCS(CC)917 T. Fujii, T. Itaya, K. Mohri, and T. Saito, *J. Chem. Soc., Chem. Commun.*, 917 (1973).

73JCS(P1)943 D. R. Sutherland, G. Tennant, and R. J. S. Vevers, *J. Chem. Soc., Perkin Trans. 1,* 943 (1973).

73JCS(P1)1903 S. M. Hecht and D. Werner, *J. Chem. Soc., Perkin Trans. 1,* 1903 (1973).

73JCS(P1)2659 A. Albert, *J. Chem. Soc., Perkin Trans. 1,* 2659 (1973).

73JHC231 A. B. DeMilo, J. E. Oliver, and R. D. Gilardi, *J. Heterocycl. Chem.* **10,** 231 (1973).

73JHC275 J. L. Singleton and M. D. Coburn, *J. Heterocycl. Chem.* **10,** 275 (1973).

73JHC755 R. Jacquier, H. Lopez, and G. Maury, *J. Heterocycl. Chem.* **10,** 755 (1973).

73JOC1095 C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.* **38,** 1095 (1973).

73JOC2247 M. H. Wilson and J. A. McCloskey, *J. Org. Chem.* **38,** 2247 (1973).

73LA578 U. Heep, *Liebigs Ann. Chem.*, 578 (1973).

73RTC711 H. C. Van der Plas and A. Koudijs, *Recl. Trav. Chim. Pays-Bas* **92,** 711 (1973).

74AHC33 T. L. Gilchrist and G. E. Gymer, *Adv. Heterocycl. Chem.* **16,** 33 (1974).

74B1913 B. Singer, L. Sun, and H. Fraenkel-Conrat, *Biochemistry* **13,** 1913 (1974).

74CPB2211 T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *Chem. Pharm. Bull.* **22,** 2211 (1974).

74JCS(P1)372 D. J. Brown and K. Ienega, *J. Chem. Soc., Perkin Trans. 1,* 372 (1974).

74JCS(P1)609 M. S. S. Siddiqui and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1,* 609 (1974).

74JOC3783 K. T. Potts and J. Kane, *J. Org. Chem.* **39,** 3783 (1974).

75AJC119 D. J. Brown and K. Ienaya, *Aust. J. Chem.* **28,** 119 (1975).

75BBR581 J. D. Engel, *Biochem. Biophys. Res. Commun.* **64,** 581 (1975) [*CA* **83,** 164479 (1975)].

75BSF857 J. Daunis and M. Follet, *Bull. Soc. Chim. Fr.*, 857 (1975).

75BSF864 J. Daunis and M. Follet, *Bull. Soc. Chim. Fr.*, 864 (1975).

75CPB54 T. Fujii, T. Itaya, and T. Saito, *Chem. Pharm. Bull.* **23,** 54 (1975).

75CPB2643 T. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, *Chem. Pharm. Bull.* **23,** 2643 (1975).

75H283 D. J. Brown and K. Ienaga, *Heterocycle* **3,** 283 (1975).

75JCS(P1)2182 D. J. Brown and K. Ienaga, *J. Chem. Soc., Perkin Trans. 1,* 2182 (1975).

75LA1934 C. Ivancsics and E. Zbiral, *Liebigs Ann. Chem.*, 1934 (1975).

75M1291 A. Sitte, R. Wessel, and H. Paul, *Monatsh. Chem.* **106,** 1291 (1975).

75M1469 G. Zigeuner, T. Strallhofer, F. Wede, and W. B. Lintschinger, *Monatsh. Chem.* **106,** 1469 (1975).

76ACH265 G. Szilagyi and H. Wambhoff, *Acta Chim. Acad. Sci. Hung.* **89,** 265 (1976) [*CA* **86,** 121238 (1977)].

76CPB655 T. Fujii, K. Sakamoto, S. Kawakatsu, and T. Itaya, *Chem. Pharm. Bull.* **24,** 655 (1976).

76KGS561 L. A. Ignatova, A. E. Gekhman, and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, 561 (1976).

76KGS706 A. N. Kost, R. S. Sagitullin, and G. G. Danagulyan, *Khim. Geterotsikl. Soedin.*, 706 (1976).

76MI1 M. Uher, V. Knoppova, and A. Martvon, *Chem. Zvesti* **30,** 514 (1976) [*CA* **87,** 151448 (1977)].

77AJC2515 D. J. Brown and T. Nagamatsu, *Aust. J. Chem.* **30,** 2515 (1977).

77BCJ2505 Y. Ogata, K. Takagi, and E. Hayashi, *Bull. Chem. Soc. Jpn.* **50,** 2505 (1977).

77CB373 G. Grenner and H. L. Schrnidt, *Chem. Ber.* **110,** 373 (1977).

77CSR43 T. K. Bradshaw and D. W. Hutchinson, *Chem. Soc. Rev.* **6,** 43 (1977).

77MI1 T. Fujii, T. Itaya, and T. Saito, *Symp. Heterocycl. (Pap.),* 129 (1977) [*CA* **89,** 163445 (1978)].

78AJC2505 D. J. Brown and T. Nagamatsu, *Aust. J. Chem.* **31,** 2505 (1978).

78BRP1534163 E. F. Rogers and R. W. Graham, Br. Pat. 1,534,163 (1978) [*CA* **91,** 74653 (1979)].

78JIC1040 A. Singh and A. S. Uppal, *J. Indian Chem. Soc.* **55,** 1040 (1978) [*CA* **90,** 203929 (1979)].

78JOC3427 R. W. Leiby, E. G. Corley, and N. D. Heindel, *J. Org. Chem.* **43,** 3427 (1978).

78JOC4951 G. L'Abbé, A. Timmerman, C. Martens, and S. Toppet, *J. Org. Chem.* **43,** 4951 (1978).

79AJC1585 D. J. Brown and T. Nagamatsu, *Aust. J. Chem.* **32,** 1585 (1979).

79JCS(P1)3107 T. Brown, K. Kadir, G. Mackenzie, and G. Shaw, *J. Chem. Soc., Perkin Trans. 1,* 3107 (1979).

79KGS262 N. V. Volkova, V. N. Konyukhov, T. G. Koksharova, L. G. Dianova, and Z. V. Pushkareva, *Khim. Geterotsikl. Soedin.*, 262 (1979).

79KGS1687 I. A. Korbukh, Yu. N. Bulychev, and M. N. Preobrazhenskaya, *Khim. Geterotsikl. Soedin.*, 1687 (1979).

79LA1872 K. Ienaga and W. Pfleiderer, *Liebigs Ann. Chem.*, 1872 (1979).

79MI1 A. Segal, U. Mate, and J. J. Solomon, *Chem.-Biol. Interact.* **28,** 333 (1979) [*CA* **92,** 158712 (1980)].

79MI2 N. N. Gulyaev, V. L. Tunitskaya, L. A. Mazurova, and E. S. Severin, *Bioorg. Khim.* **5,** 552 (1979) [*CA* **92,** 6852 (1980)].

80IJC(B)115 S. S. Sangapure and Y. S. Agasimundin, *Indian J. Chem., Sect. B* **19B,** 115 (1980) [*CA* **93,** 186280 (1980)].

80JCR(S)308 D. R. Buckle, *J. Chem. Res., Synop.,* 308 (1980) [*CA* **94,** 15656 (1981)].

80JCS(P1)1013 H. Singh and P. Singh, *J. Chem. Soc., Perkin Trans. 1,* 1013 (1980).

80MI1 J. Wierzchowski, J. Kusmierek, J. Giziewicz, D. Salvi, and D. Shugar, *Acta Biochim. Pol.* **27,** 35 (1980) [*CA* **94,** 65608 (1981)].

80PAC1611 M. Tisler, *Pure Appl. Chem.* **52,** 1611 (1980).

81ABC2631 Y. Yamazaki and H. Maeda, *Agric. Biol. Chem.* **45,** 2631 (1981).

81CB937 W. Bornatsch, H. Reel, and K. H. Schuendehuette, *Chem. Ber.* **114,** 937 (1981).

81CB2056 F. Seela and W. Bussmann, *Chem. Ber.* **114,** 2056 (1981).

81H1049 H. Inoue, S. Takada, S. Tanigawa, and T. Ueda, *Heterocycles* **15,** 1049 (1981).

81JHC43 C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthar, and V. S. Bhadti, *J. Heterocycl. Chem.* **18,** 43 (1981).

81JOC3949 K. Hirota, Y. Kitade, and S. Senda, *J. Org. Chem.* **46,** 3949 (1981).

81KGS1264 N. V. Abbakumova, Yu. G. Putsykin, Yu. A. Baskakov, and Yu. A. Kondrat'ev. *Khim. Geterotsikl. Soedin.,* 1264 (1981).

81MI1 A. F. Bueckmann, M. R. Kula, R. Wichmann, and C. Wandrey, *J. Appl. Biochem.* **3,** 301 (1981) [*CA* **96,** 158090 (1982)].

81MI2 N. N. Guseva, A. E. Gekhman, L. A. Ignatova, and B. V. Unkovskii, *Deposited Doc. SPSTL* Khp-D81, 872 (1981) [*CA* **98,** 89307Z (1983)].

81T4353 M. Legraverend, J. M. Lhoste, and E. Bisagni, *Tetrahedron* **37,** 4353 (1981).

82JAP(K)57/139094 Agency of Industrial Sciences and Technology, Jpn. Kokai Pat. 57/139094 (1982) [*CA* **98,** 89817 (1983)].

82JHC943 M. T. Nguyen, G. Leroy, M. Sana, and J. Elguero, *J. Heterocycl. Chem.* **19,** 943 (1982).

83CPB3149 T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, *Chem. Pharm. Bull.* **31,** 3149 (1983).

83GEP3204126 M. Mardin, R. Sundermann, F. Hoffmeister, W. D. Busse, H. Horstmann, and S. Raddatz, Ger. Pat. 3,204,126 (1983) [*CA* **99,** 175781 (1983)].

83JCS(P1)1293 K. Hirota, Y. Kitade, K. Shimada, S. Senda, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1,* 1293 (1983).

83JPT113 J. E. Reimann, P. G. Grant, R. W. Colman, and R. F. Colman, *J. Protein Chem.* **2,** 113 (1983) [*CA* **99,** 176206 (1983)].

83M581 K. Schweiger, *Monatsh. Chem.*. **114,** 581 (1983).

83YZ594 T. Higashino, S. Yoshida, and E. Hayashi, *Yakugaku Zasshi* **103,** 594 (1983) [*CA* **99,** 105184 (1983)].

84CHEC94 A. R. Katritzky and J. M. Logvoski, *Compr. Heterocycl. Chem.* **5,** 94 (1984).

84IJC(B)870 A. K. Sen and A. K. Mukhopadhyay, *Indian J. Chem., Sect. B* **23B,** 870 (1984) [*CA* **102,** 954455 (1985)].

84JCS(P1)1859 K. Hirota, Y. Kitade, and S. Senda, *J. Chem. Soc., Perkin Trans. 1,* 1859 (1984).

84MI1 F. Seela and W. Bussmann, *Nucleosides Nucleotides* **3,** 195 (1984).

84PJC85 R. Balicki, *Pol. J. Chem.* **58,** 85 (1984) [*CA* **103,** 53925 (1985)].

85CPB3635 T. Fujii and T. Saito, *Chem. Pharm. Bull.* **33,** 3635 (1985).

85CS227 A. Joergensen, K. A. M. El-Bayouki, and E. B. Pedersen, *Chem. Scr.* **25,** 227 (1985).

85JCS(P1)1137 K. Hirota, K. Banno, Y. Yamada, and S. Senda, *J. Chem. Soc., Perkin Trans. 1,* 1137 (1985).

85JHC831 C. J. Shishoo, M. B. Devani, G. V. Ullas, S. Ananthan, and V. S. Bhadti, *J. Heterocycl. Chem.* **22,** 831 (1985).

85JOC1512 K. Hirota, Y. Kitade, K. Shimada, and Y. Maki, *J. Org. Chem.* **50,** 1512 (1985).

85MI1 T. Fujii and T. Saito, *Nucleic Acids Symp. Ser.* **16,** 69 (1985) [*CA* **105,** 60871 (1986)].

85MI2 I. Honda and Y. Shimomura, *Fukui Daigaku Kogakubu Kenkyu Hokoku* **33,** 185 (1985) [*CA* **108,** 37792 (1988)].

85PHA54 K. Kottke, H. Kuehmstedt, and D. Knoke, *Pharmazie* **40,** 54 (1985).

85T2237 H. C. Van der Plas, *Tetrahedron* **41,** 2237 (1985).

85TL2905 D. Ranganathan, F. Farooqui, and D. Bhattacharyya, *Tetrahedron Lett.* **26,** 2905 (1985).

86BBA64 J. Salord, C. Tarnus, C. D. Muller, and F. Schuber, *Biochim. Biophys. Acta* **886,** 64 (1986) [*CA* **105,** 11910 (1987)].

86CB1070 H. Wamhoff and H. A. Thiemig, *Chem. Ber.* **119,** 1070 (1986).

86CPB1094 T. Fujii, T. Saito, and N. Terahara, *Chem. Pharm. Bull.* **34,** 1094 (1986).

86CS337 F. Johannsen, A. Joergensen, K. A. M. El-Bayouki, and E. B. Pedersen, *Chem. Scr.* **26,** 337 (1986).

86CS639 K. Bogdanowicz-Szwed and M. Lipowska, *Chem. Scr.* **26,** 639 (1986).

86JCS(P1)2163 D. Korbonits and P. Kolonits, *J. Chem. Soc., Perkin Trans. 1,* 2163 (1986).

86JHC1189 J. L. Kelley and E. W. McLean, *J. Heterocycl. Chem.* **23,** 1189 (1986).

86MI1 J. Beres, Y. C. Lee, D. I. Brixner, J. I. Olsen, and M. P. Schweizer, *Nucleosides Nucleotides* **5,** 1 (1986).

86MI2 I. Honda and Y. Shimomura, *Fukui Daigaku Kogakubu Kenkyu Hokoku* **34,** 25 (1986) [*CA* **108,** 5976 (1987)].

86MI3 M. Eto and S. Kawasaki, *Nucleic Acids Symp. Ser.* **17,** 65 (1986) [*CA* **107,** 134607 (1987)].

86MI4 M. Herrmann and J. Schmidt, *Zfl-Mitt.* **115,** 169 (1986) [*CA* **106,** 155768 (1987)].

86MI5 I. Honda and Y. Shimomura, *Fukui Daigaku Kogakubu Kenkyu Hokoku* **34,** 173 (1986) [*CA* **107,** 175998 (1987)].

86T4481 D. Ranganathan, F. Farooqui, D. Bhattacharyya, S. Mehrotra, and K. Kesavan, *Tetrahedron* **42,** 4481 (1986).

86TL3127 O. Rousseaux, D. Blondeau, and H. Sliwa, *Tetrahedron Lett.* **27,** 3127 (1986).

87BCJ4115 H. Yamamoto, C. Ohira, T. Aso, and W. Pfleiderer, *Bull. Chem. Soc. Jpn.* **60,** 4115 (1987).

87CCC2260 M. Dzurilla, P. Kutschy, and D. Koscik, *Collect. Czech Chem. Commun.* **52,** 2260 (1987).

87CPB4482 T. Fujii, T. Saito, T. Itaya, K. Kizu, Y. Kumazawa, and S. Nakajima, *Chem. Pharm. Bull.* **35,** 4482 (1987).

87JA1275 X. Gao and R. A. Jones, *J. Am. Chem. Soc.* **109,** 1275 (1987).

87MI1 I. Honda and Y. Shimomura, *Fukui Daigaku Kogakubu Kenkyu Hokoku* **35,** 163 (1987) [*CA* **108,** 5975 (1988)].

87MI2 I. Honda and Y. Shimomura, *Fukui Daigaku Kogakubu Kenkyu Hokoku,* **35,** 233 (1987) [*CA* **108,** 221673 (1988)].

87PHA412 M. Schleuder, K. Kottke, H. Kuehmstedt, and I. Szkorupa, *Pharmazie* **42,** 412 (1987).

87S466 S. Leistner, M. Guetschow, and G. Wagner, *Synthesis,* 466 (1987).

88BSB179 G. L'Abbé, W. Meutermans, L. Van Meervelt, G. S. D. King, and A. T. H. Lenstra, *Bull. Soc. Chim. Belg.* **97,** 179 (1988).

88BSB543 G. L'Abbé, A. Vandendriessche, G. Van Essche, and S. Toppet, *Bull. Soc. Chim. Belg.* **97,** 543 (1988).

88CS195 J. Mogensen, A. Joergensen, and E. B. Pedersen, *Chem. Scr.* **28,** 195 (1988).

88H1145 T. Fujii, T. Saito, and S. Mori, *Heterocycles* **27,** 1145 (1988).

88JPR289 C. Bischoff and E. Schroeder, *J. Prakt. Chem.* **330,** 289 (1988).
88M11 I. Honda and Y. Shimomura, *Fukui Daigaku Kogakubu Kenkyu Hokoku* **36,** 165 (1988) [*CA* **111,** 6684 (1988)].
88PS55 D. Briel, J. Sieler, G. Wagner, and W. Schade, *Phosphorus Sulfur* **35,** 55 (1988).
88S851 R. T. Chakrasali, H. Ila, and H. Junjappa, *Synthesis,* 851 (1988).
89BSB343 G. L'Abbé, M. Bruynseels, L. Beenaerts, A. Vandendriessche, P. Delbeke, and S. Toppet, *Bull. Soc. Chim. Belg.* **98,** 343 (1989).
89BSB879 G. L'abbé, K. Buelens, W. Franek, and P. Delbeke, *Bull. Soc. Chim. Belg.* **98,** 879 (1989).
89CPB2008 K. Hirota, H. Sajiki, Y. Kitade, and Y. Maki, *Chem. Pharm. Bull.* **37,** 2008 (1989).
89CZ11 H. Wamhoff and W. Wambach, *Chem.-Ztg.* **113,** 11 (1989) [*CA* **111,** 194677 (1990)].
89JCS(P1)1695 K. Hirota, H. Sajiki, Y. Kitade, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1,* 1695 (1989).
89JHC687 H. Sliwa, D. Blondeau, and O. Rousseaux, *J. Heterocycl. Chem.* **26,** 687 (1989).
89JHC1811 G. L'Abbé and E. Vanderstede, *J. Heterocycl. Chem.* **26,** 1811 (1989).
89LA931 R. Spitzner, J. Andersch, and W. Schroth, *Liebigs Ann. Chem.,* 931 (1989).
89M781 H. Junek, M. Klade, and H. Sterk, *Monatsh. Chem.* **120,** 781 (1989).
90AP857 S. Leistner, M. Guetschow, and J. Stach, *Arch. Pharm. (Weinheim. Ger.)* **323,** 857 (1990).
90AQ62 A. A. Elagamey and M. A. Sofan, *An. Quim.* **86,** 62 (1990) [*CA* **114,** 42713 (1991)].
90CB1575 D. Moderhack, K. H. Goos, and L. Preu, *Chem. Ber.* **123,** 1575 (1990).
90CPB652 T. Fujii, T. Saito, T. Sakuma, M. Minami, and I. Inoue, *Chem. Pharm. Bull.* **38,** 652 (1990).
90CPB1392 T. Fujii, T. Saito, and Y. Kumazawa, *Chem. Pharm. Bull.* **38,** 1392 (1990).
90CPB1536 T. Saito, I. Inoue, and T. Fujii, *Chem. Pharm. Bull.* **38,** 1536 (1990).
90CPB2591 T. Fujii, T. Saito, and S. Sori, *Chem. Pharm. Bull.* **38,** 2591 (1990).
90CPB3326 T. Fujii, T. Saito, H. Hisata, and K. Shinbo, *Chem. Pharm. Bull.* **38,** 3326 (1990).
90H1593 T. Saito, H. Hayashibara, Y. Kumazawa, T. Fujisawa, and T. Fujii, *Heterocycles* **31,** 1593 (1990).
90IJC(B)1070 P. Sukumaran and K. N. Rajasekharan, *Indian J. Chem., Sect. B* **29B,** 1070 (1990) [*CA* **114,** 122254 (1991)].
90IJC(B)1074 P. Sukumaran and K. N. Rajasekharan, *Indian J. Chem., Sect. B* **29B,** 1074 (1990) [*CA* **114,** 122222 (1991)].
90JA1247 J. Adler, W. Powell, and R. Wolfenden, *J. Am. Chem. Soc.* **112,** 1247 (1990).
90JCS(P1)123 K. Hirota, H. Sajiki, Y. Kitade, and Y. Maki, *J. Chem. Soc., Perkin Trans 1,* 123 (1990).
90JCS(P1)367 K. Hirota, Y. Kitade, H. Sajiki, Y. Maki, and M. Yogo, *J. Chem. Soc., Perkin Trans. 1,* 367 (1990).

90JHC391 K. C. Liu, B. J. Shih, and J. W. Chern, *J. Heterocycl. Chem.* **27,** 391 (1990).

90JHC1441 J. Liebscher, A. Hassoun, H. Van der Plas, and C. Stam, *J. Heterocycl. Chem.* **27,** 1441 (1990).

90JHC1649 B. Bouteau, J. C. Lancelot, and M. Robba, *J. Heterocycl. Chem.* **27,** 1649 (1990).

90JIC260 T. Raj and S. Y. Ambekar, *J. Indian Chem. Soc.* **67,** 260 (1990) [*CA* **113,** 115243 (1990)].

90JPR387 E. Fanghaenel, B. Kordts, A. M. Richter, and K. Dutschmann, *J. Prakt. Chem.* **332,** 387 (1990).

90MI1 K. C. Liu and B. J. Shih, *Chung-hua Yao Hsueh Tsa Chih* **42,** 391 (1990) [*CA* **114,** 143268 (1991)].

90PHA30 K. Kottke, H. Kuehmstedt, I. Graefe, D. Knoke, and M. Schleuder, *Pharmazie* **45,** 30 (1990).

90T3431 K. Hirota, H. Sajiki, P. Z. Ni, Y. Kitade, and Y. Maki, *Tetrahedron* **46,** 3431 (1990).

91ABC1999 M. Eto, M. Iio, H. Omura, and M. Eto, *Agric. Biol. Chem.* **55,** 1999 (1991).

91CCC1287 M. Dzurilla, P. Kutschy, J. Imrich, D. Koscik, and R. Kraus, *Collect. Czech Chem. Commun.* **56,** 1287 (1991).

91CPB301 T. Fujii, T. Saito, K. Kizu, H. Hayashibara, Y. Kumazawa, S. Nakajima, and T. Fujisawa, *Chem. Pharm. Bull.* **39,** 301 (1991).

91HCA899 V. I. Ognyanov and M. Hesse, Helv. *Chim. Acta* **74,** 899 (1991).

91IJC(B)740 H. Singh, P. Aggarwal, and S. Kumar, *Indian J. Chem., Sect. B* **30B,** 740 (1991) [*CA* **115,** 182352 (1991)].

91JHC1709 K. Vaughan, R. J. Lafrance, Y. Tang, and D. L. Hooper, *J. Heterocycl. Chem.* **28,** 1709 (1991).

91JPR107 F. Tittelbach, *J. Prakt. Chem.* **333,** 107 (1991).

91MI1 M. K. Hu, Li. Y. Hsu, and K. C. Liu, *Chung-hua Yao Hsueh Tsa Chih* **43,** 151 (1991) [*CA* **115,** 71526 (1991)].

91MI2 F. G. Ott and E. Schlimme, *Kiel. Milchwirtsch. Forschungsber.* **43,** 213 (1991) [*CA* **116,** 127266 (1992)].

91MI3 P. Pazdera and V. Potucek, *Chem. Pap.* **45,** 677 (1991) [*CA* **116,** 59312 (1992)].

91TL97 T. Fujii, T. Saito, S. Mori, and J. Chikazawa, *Tetrahedron Lett.* **32,** 97 (1991).

92CPB357 N. Suzuki, T. Miwa, S. Aibara, H. Kanno, H. Takamori, M. Tsubokawa, Y. Ryokawa, W. Tsukada, and S. Isoda, *Chem. Pharm. Bull.* **40,** 357 (1992).

92CPB2839 K. Hirota, P. Z. Ni, A. Suzuki, H. Takasu, Y. Kitade, and Y. Maki, *Chem. Pharm. Bull.* **40,** 2839 (1992).

92H1573 A. Lorente, M. L. Garcia, M. Fernandez, and J. L. Soto, *Heterocycles* **34,** 1573 (1992).

92IJC(B)142 H. Singh, P. Aggarwal, and S. Kumar, *Indian J. Chem., Sect. B* **31B,** 142 (1992) [*CA* **116,** 173311 (1992)].

92JOC190 A. R. Katritzky, F. B. Ji, W. Q. Fan, J. K. Gallos, J. V. Greenhill, R. W. King, and P. J. Steel, *J. Org. Chem.* **57,** 190 (1992).

92JOM213 H. Poleschner, R. Radeglia, and J. Fuchs, *J. Organomet. Chem.* **427,** 213 (1992).

92KGS225 G. G. Danagulyan, G. Saakyan, and M. G. Zalinyan, *Khim. Geterotsikl. Soedin,*. 225, (1992).

92MI1 M. Potacek and H. Zornova, *Chem. Pap.* **46,** 34 (1992) [*CA* **118,** 59660 (1993)].

92MI2 P. Pazdera, J. Meindl, and E. Novacek, *Chem. Pap.* **46,** 322 (1992) [*CA* **118,** 233991 (1993)].

93CPB453 T. Saito, M. Murakami, T. Inada, H. Hayashibara, and T. Fujii, *Chem. Pharm. Bull.* **41,** 453 (1993).

93CPB1850 T. Saito, T. Kanai, and T. Fujii, *Chem. Pharm. Bull.* **41,** 1850 (1993).

93JHC435 C. J. Shishoo and K. S. Jain, *J. Heterocycl. Chem.* **30,** 435 (1993).

93JHC849 M. F. G. Stevens, W. K. Chui, and M. A. Castro, *J. Heterocycl. Chem.* **30,** 849 (1993).

93JHC1607 B. Riemer, A. Hassoun, J. Liebscher, P. G. Jones, and A. Chrapkowski, *J. Heterocycl. Chem.* **30,** 1607 (1993).

93KGS124 L. I. Belenkii, D. M. Antonov, A. A. Dudinov, E. D. Lubuzh, and M. M. Krayushkin, *Khim. Geterotsikl. Soedin.*, 124 (1993).

93KGS1545 G. G. Danagulyan, L. G. Saakyan, G. A. Bulakhov, and P. B. Terentyev, *Khim. Geterotsikl Soedin.*, 1545 (1993).

94CPB382 T. Fuji, T. Saito, R. Ii, and T. Suzuki, *Chem. Pharm. Bull.* **42,** 382 (1994).

94CPB739 J. Toda, M. Seki, K. Amano, T. Dyama, T. Sano, F. Kiuchi, and Y. Tsuda, *Chem. Pharm. Bull.* **42,** 739 (1994).

94MI1 H. A. Etman, *Alexandria J. Pharm. Sci.* **8,** 150 (1994) [*CA* **122,** 5591 (1995)].

94MI2 H. A. Etman and A. A. Fadda, *Alexandria J. Pharm. Sci.* **8,** 187 (1994) [*CA* **123,** 339648 (1995)].

95H1197 R. F. de Boer, D. G. I. Petra, M. J. Wanner, A. Boesaart, and G. Koomen, *Heterocycles* **41,** 1197 (1995).

95JAP(K)07/149698 T. Mizuno and T. Shiozaki, Jpn. Kokai Pat., 07/149,698 (1995) [*CA* **123,** 285571 (1995)].

95JOC2251 L. De Napoli, A. Messere, D. Montesarchio, and G. Piccialli, *J. Org. Chem.* **60,** 2251 (1995).

95MI1 D. Martin, C. Kiesner, and E. Schlimme, *Kiel. Milchwirtsch. Forschungsber.* **47,** 75 (1995) [*CA* **123,** 226409 (1995)].

95TL5637 E. Laskos, P. S. Lianis, N. A. Rodios, A. Terzis, and C. P. Raptopoulou, *Tetrahedron Lett.* **36,** 5637 (1995).

98AHC(57) E. S. H. El Ashry and N. Rashed, *Adv. Heterocycl. Chem.* **71,** 57 (1998).

99AHC(127) E. S. H. El Ashry and N. Rashed, *Adv. Heterocycl. Chem.* **72,** 127 (1999).

98ZN1203 E. S. H. El Ashry, Y. El Kilany, N. Rashed, A. Mousaad, and H. Assafir, *Z. Naturforsch.*, **53b,** 1203 (1998).

ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 75

Recent Advances in the Chemistry of Pyridazines

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I. Introduction

This chapter covers further advances in pyridazine chemistry since the last chapter in this series was published (90AHC385). In general, it includes references through mid-1998, although articles from some important journals have been included until the end of 1998.

Since the late 1980s many bioactive natural products containing pyridazine rings as a part of their molecules have been discovered and their structures determined. It is surprising how many new synthetic approaches and unusual transformations of pyridazines have been described. Also,

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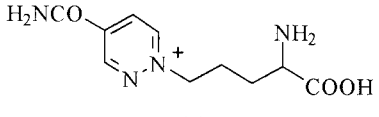
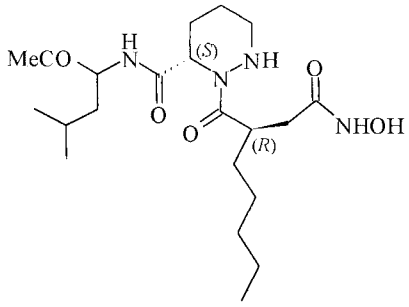
other aspects have been the subject of intensive investigations, from a theoretical standpoint, of biological activities. With the resurgence of pyridazine derivatives as novel bioactive molecules these were the subject of intensive synthetic and medicinal studies. Since the length of this chapter is limited we decided to omit the chemistry of pyridazine complexes with inorganic ions or compounds as well as their biological activities.

II. Natural Products

Although in the past pyridazine natural products were rather rare, since the late 1980s a significant number of such compounds was discovered. They contain as a rule partially or completely saturated pyridazine rings. An ester of 4-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid, which is a constituent of luzopeptins, the dimeric antitumor cyclodecadepsipeptide antibiotic was prepared in a five-step synthesis as racemate [94JCS(CC)1867]. Pyridazomycin **1,** a fungicide antibiotic, produced by *Streptomyces violaceoniger,* is a quaternized pyridazine with an amino acid side-chain. It is proposed that its biosynthesis starts from glycine and ornithin(94AG1733). The free carboxylic acid is the first reported natural product that appears to act via reversible oxidation/reduction linked to photosynthesis electron transport (97MI1). Maleic acid hydrazide metabolite, its 1-glucosyl derivative, was isolated from tobacco plant (95MI3). A series of piperazic acid-based stromelysin (MMP-3) inhibitors was synthesized (95BMC3053) and the structure of a new peptide antibiotic **2,** YM-24074, was elucidated (96JAN811). As a part of the 19-membered cyclodepsipeptide ring system a hexapeptide unit with two piperazic acid molecules has been synthesized in a multistep synthesis (94TL7685).



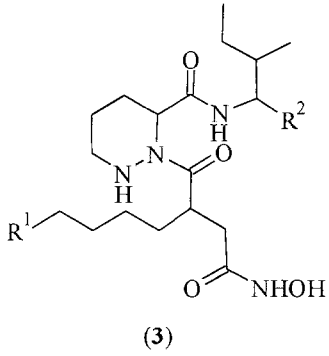
(1)



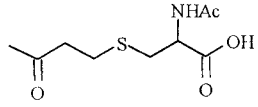
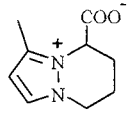
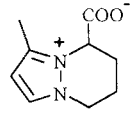
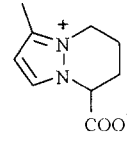
(2)

Antrimycins (cirratiomycins are the same substances) are linear polypeptide antibiotics (from *Streptomyces xanthocidicus* and *St. ciratus*) containing in the central part (3*S*)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid. Syntheses of this acid have been developed (91CL1953; 93S809) and the total synthesis of antrimycin D_v was described [92JCS(CC)1186].

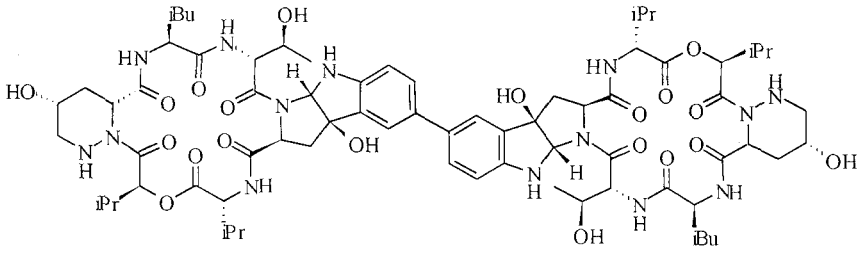
From *Actinomadura atramentaria* five matlystatins (A, B, D, E, F) were isolated and their structures **3** elucidated (92JAN1723; 94JAN1473, 94JAN1481). They are new inhibitors of type IV collagenases and total syntheses of compounds A (93TL8477) and B (93TL683; 94JAN1481) have been described.



(**3**)

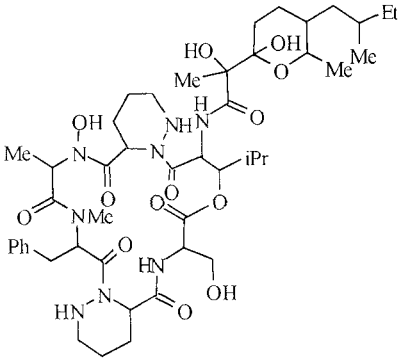
	R^1	R^2
A :	Me	
B :	Me	COEt
D :	Me	
E :	H	
F :	Me	

The antitumor antibiotic himastatin **4** (from *Streptomyces hygroscopicus*) is a unique dimeric molecule joined through a biphenyl linkage. Each of the 18-membered rings contains (3*R*,5*R*)-5-hydroxypiperazic acid (96JAN299). A recent revision of the stereochemical assignment and total synthesis of **4**



(4)

were published [98AG(E)2993, 98AG(E)2995]. Several hexadepsipeptide antibiotics are 19-membered ring compounds. Antibiotics variapeptin **5** and citropeptin **6** contain two molecules of piperazic acid (90JAN477) as well as aurantimycins A, B, and C **7** (from *Streptomyces aurantiacus*). For compound A X-ray diffraction analysis was made (95JAN119). From the culture broth of *Actinomadura verrucosospora* verucopeptin **8** was isolated. The 19-membered cyclic peptide incorporates one molecule of hexahydropyridazine-3-carboxylic acid (93JAN921, 93JAN928). The D- and L-piperazic acids are incorporated in the 19-membered hexadepsipeptide antibiotic L-156,602 (from *Streptomyces sp.*) (91JAN249) and two molecules of piperazic acid are also present in the related cyclic antibiotics IC101 **9** (from *Streptomyces albulus*) (93JAN1658) and A83586C. The first asymmetric total synthesis of the later was recently accomplished [97JCS(CC)2319].



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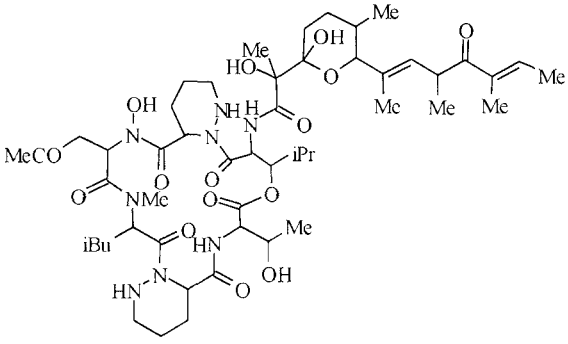

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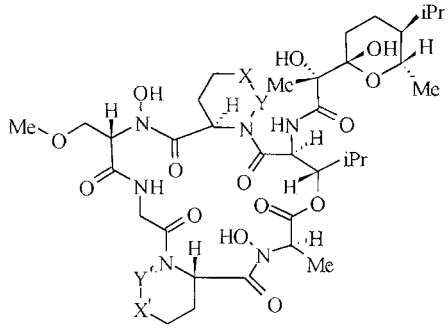
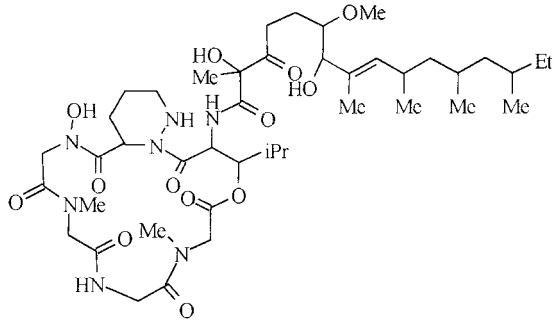


(7)

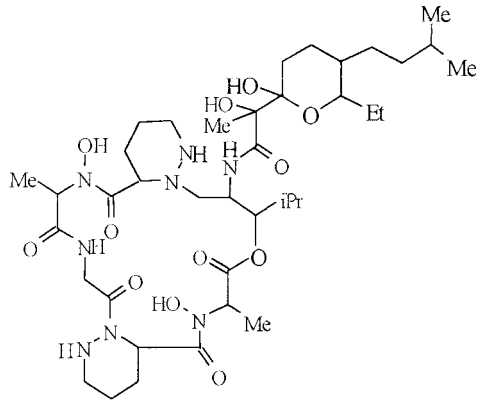
Aurantimycin A : X-Y = X'-Y' : -CH_2-NH-

B : X-Y : -CH_2-NH-; X'-Y' : -CH=N-

C : X-Y = X'-Y' : -CH=N-



(**8**)



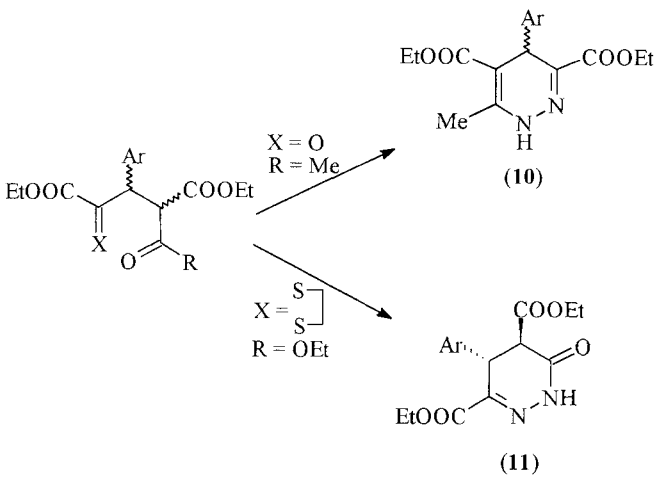
(**9**)

III. Synthetic Methods

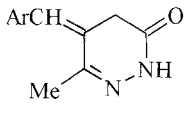
A. From Carbonyl Compounds

1,4-Diketones and γ-keto esters remain standard starting compounds for the preparation of pyridazines in the search of biologically active compounds. Acetylenic 1,4-diketones were transformed in low yield into 4(1*H*)-pyridazinones, existing actually as 4-hydroxypyridazines based on spectroscopic evidence. The main products were pyrazoles (92MI2; 93RRC989). Pyridazine fatty esters were obtained from methyl 9,12-dioxostearate and hydrazine by ultrasonic irradiation [97JCS(P1)3485] and pyridazineestradiol derivatives were obtained from estradiol, substituted at position 2 with unsaturated diketones (96AP433).

2,3,4,5-Tetrahydro-3-pyridazinones were prepared from 4-aryl-4-ketobutyric acids (β-benzoylpropionic acids) or their esters (88FA539, 88JHC1689; 90JHC557, 90JMC1735, 90PHA724; 91JOC1963, 91MI8; 92PHA249; 95JMC4878, 95JMC4880; 96ZOR591). 4-Pyrazolonyl analogs reacted similarly; after the pyridazine cyclization the pyrazolone ring is eliminated (93RRC213). From 3-benzoyl-3-butenoic acids and hydrazine, 6-aryl-5-methyl-3(2*H*)-pyridazinones were formed in low yield since the major products were 4-pyrazoleacetic acids (90JHC205). The 1,4-dihydro structure was claimed for the 4-nitroarylpyridazines obtained from nitroaryl γ-keto esters. They were oxidized with activated MnO_2 to the aromatic pyridazines (93CPB156). These were also obtained from α-hydroxy-γ-ketoacids [89H(29)1907]. The unprotected bis-keto ester afforded also a 1,4-dihydropyridazine derivative **10,** whereas from its dithiolane derivative, the tetrahydropyridazine **11,** was formed (89JHC1353). 6-Substituted



3(2*H*)-pyridazinones were obtained in a one-pot reaction after a known process from acetophenone, glyoxylic acid, and hydrazine in moderate to good yields. The reaction proceeds via an aldol intermediate (93S334). 6-(9-Anthracenyl)-3(2*H*)-pyridazinone was prepared from *β*-(9-anthracenoyl) acrylic acid (91MI4). Pyridazinones **12** were prepared from 3-arylidene-4-oxopentanoic acids and the tautomeric form **13** was excluded based on NMR evidence (90CPB3009). 5-Arylidene-4-oxo pentanoic acids yielded 6-arylethenyl-3(2*H*)-pyridazinone derivatives (89JMC342). Recent investigations, however, support the aromatic structure **13** (95AJC1601).



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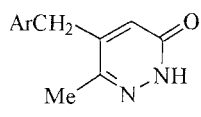

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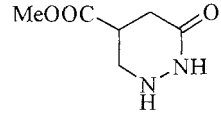
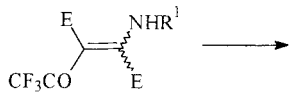


(14)

Perhydro-pyridazine-3,6-diones were prepared from succinic anhydride or its methyl analog with hydrazine or monosubstituted hydrazines under microwave irradiation with reaction times drastically reduced and yields comparable to standard procedures (96TL4145). The addition of hydrazine hydrate at room temperature to dimethyl methylenesuccinate gave also a pyridazine derivative **14** as evidenced from X-ray analysis. Evidently the cyclization reaction involved the methylene and methoxycarbonyl group [93JCS(P1)1931]. Acyl hydrazides and maleoyl dichloride afforded 2-aroyl-6-hydroxy-3(2*H*)-pyridazinones (97MI5) and 4-hydroxy-3(2*H*)-pyridazinone derivatives **16** were prepared from butenedioates **15** (as a mixture of *E* and *Z* isomers, the *Z* isomer prevailing). The butenedioates were obtained from addition of amines to dimethyl acetylenedicarboxylate according to a reported procedure. The structures of **16** were determined using 2D NMR and ^{15}N-NMR techniques (93JHC1501). A novel synthetic approach is a one-pot procedure involving succinic or maleic acid and *in situ* formed diazaphosphole derivative from a hydrazone and PCl_3. From succinic acid the perhydro derivatives **17** and from maleic acid the corresponding 1,2-dihydro-3,6-pyridazinediones were obtained (96T13695).



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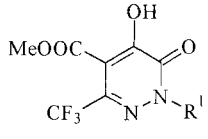

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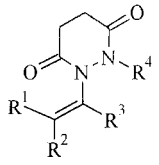
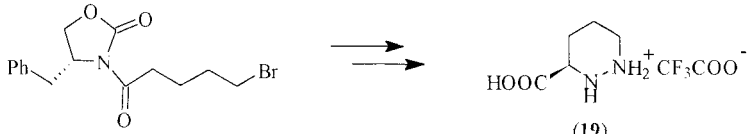


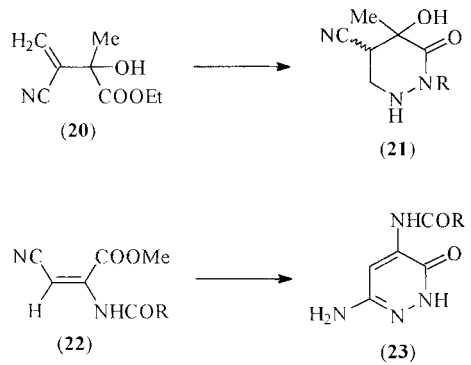
(17)

Several pyridazine derivatives were prepared from haloalkyl or cyanoalkyl ketones. Chloroalkyl ketones, prepared from 4-chlorobutyryl chloride and phenols, gave with excess of hydrazine 3-aryl 1,4,5,6-tetrahydropyridazines (88SC2183). Ethyl 1,6-dihydropyridazine 3-carboxylate was obtained from δ-bromo allylic α-keto ester with *p*-toluenesulfonylhydrazine at room temperature (96T14975). A convenient asymmetric synthesis of (3*R*)- **19** and (3*S*)-piperazic acid from a chiral bromovaleryl carboximide enolate **18** with di-*tert*-butyl azodicarboxylate is reported. The trifluoroacetate salt of **19** was obtained with a diastereoselectivity greater than 96% (92TL7613). The same reaction was used to prepare the protected *S*- isomer of **19** on larger scale (95SL615). In view of the criticism (95SL615) of the previously described procedure of **19** and the 3*S* isomer, the synthesis has been reinvestigated and the previous results confirmed.



(18) (19)

The reaction paths have been investigated in detail (96T1047). A self-condensation product of ω-bromoacetophenone, when treated with potassium thiocyanate and subsequently with phenylhydrazine, afforded 1,3,5-triphenyl-4-thiocyanato-1,6-dihydropyridazine [88CI(L)30]. 1,3-Diaryl or otherwise substituted 1,3-cyanoketones were the starting material for the preparation of 4,5-dihydropyridazines (93JHC1093, 93SC1371). The substituted cyanoacrylonitrile **20** was transformed into **21** (stereochemistry was not determined) (92TL7345) and the propenoates **22** (R=Me or Ph) afforded at room temperature **23** (98HCA231). From 4-aryl-3-bis(methyl-



(20) (21)

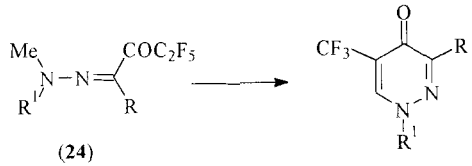
(22) (23)

thio)methylene-4-oxobutanenitriles, 6-aryl-5-bis(methylthio)methyl3(2*H*)-pyridazinones were prepared (88S89).

A great number of pyridazines was prepared from preformed hydrazones or related compounds. Hydrazones of 1,2-diketones, when treated with ethyl cyanoacetate, were transformed into cyanopyridazinones (88LA1005; 95HAC469, 95T12745). The transformation is accelerated under the influence of microwave irradiation (95HAC469). A tetrasubstituted pyridazine was prepared from benzyl monohydrazone and α-ketoglutaric acid in the presence of triethylamine (95PJC685). 3(2*H*)-Pyridazinones were obtained with variable yields in a one-pot reaction from phenylhydrazones of 1,2-diketones and trimethylsilyl acetate with *n*-BuLi in THF at –78°C, followed by heating at 40–45°C (91SC1935). In another variant, phenylhydrazones of 1,2-dicarbonyl compounds were treated with triethyl phosphonoacetate in the presence of NaH as a catalyst to give 2-phenyl-3(2*H*)-pyridazinones (91SC1021). In a related transformation the Wittig reagents were used and a mechanistic interpretation was given [97JCR(S)236]. Hydrazones, prepared from symmetrical 1,2-diketones and 1,1,1-trifluoro-3-phenylsulfonyl-2-propanone hydrazone were cyclized with either NaOMe/MeOH or LDA to 5,6-disubstituted 4-hydroxy-3-trifluoromethylpyridazines (93H909). 3,4-Diphenyl-5-cyano-6(1*H*)-pyridazinethione can be prepared by three routes, one of them involves the reaction of benzyl hydrazone with cyanothioacetamide [91PS(56)81]. Hydrazones of aryl trifluoromethyl 1,2-diketones underwent acid-catalyzed self-condensation (in refluxing TFA) to give 3,6-diaryl-4,5-bis(trifluoromethyl)pyridazines. A tentative mechanistic interpretation of this unusual synthesis is presented (98H2221).

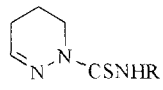
3-Arylhydrazones of pentane-2,3,4-trione, when treated with NaH and acetyl chloride or chloroacetyl chloride, were transformed into 1-aryl-4(1*H*)-pyridazinones or 2-aryl-3(2*H*)-pyridazinones, respectively [91IJC(B)932; 92IJC(B)273].

Pyridazine derivatives were also obtained from hydrazones of ketoglutarate [94H(37)401] or benzaldehyde arylhydrazones after treatment with allyl bromide to give perhydropyridazines (96JHC213). Arylhydrazones of 2,3-dichloro-4-oxo-2-butenoic acid gave in acetic anhydride 2-aryl-4,5-dichloro-3(2*H*)-pyridazinones (90CCC2707). 5-Trifluoromethyl-4(1*H*)-pyridazinones are obtainable from aldehyde dialkylhydrazones, which gave with pentafluoropropionic anhydride (better than TFAA) **24,** and cyclization to **25** was achieved when **24** were absorbed on silica gel and heated at 70–90°C (93TL5135). With trichloroacetyl chloride in pyridine related 4(1*H*)-pyridazinones were formed (90S467). Thiosemicarbazones of γ-chlorobutyrophenone, when cyclized in the presence of powdered KOH in dichloromethane at room temperature, gave the corresponding pyri-



(24) (25)

dazinethiocarboxamides **26** (90JHC707). A chlorohydrazone **27,** when treated with excess of ethyl vinyl ether, afforded **28,** which after treatment with TFA at room temperature gave a mixture of **29** and **30** (major product). Deprotection at N1 of **30** with K_2CO_3/MeOH gave the fully aromatic pyridazine derivative [91JCS(P1)3361].



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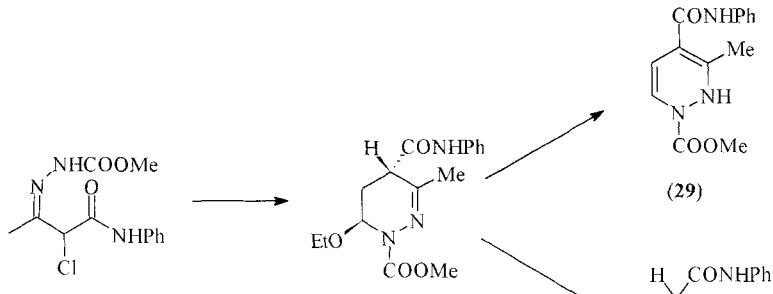
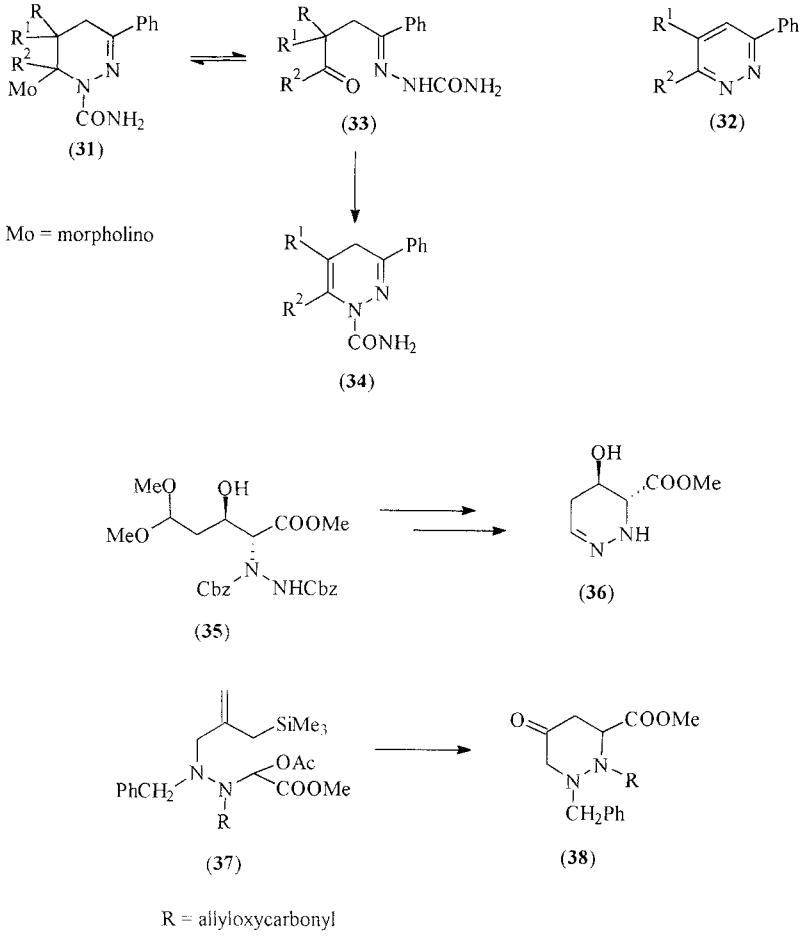


(27) (28) (29) (30)

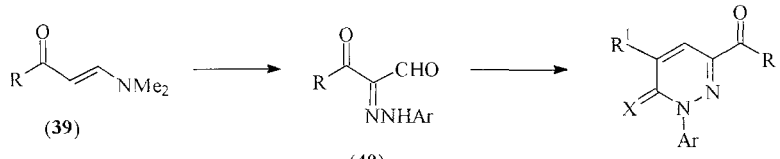
There are some special synthetic approaches as, for example, the reaction between morpholinoenamines of aldehydes and the semicarbazone of ω-bromoacetophenone to give **31.** On the other hand, enamines of acyclic ketones gave **32** or **31.** In solution **31** is in fast equilibrium with the open-chain compound **33.** If traces of acid are added the equilibrium disappears and **34** is formed (88G187). The tetrahydro compound **36** was prepared from **35** after hydrogenolysis and treatment with TFA (98SL1279). Glyoxylate adduct

of N-alkylated allyoxycarbonyl carbazate **37** was cyclized in the presence of $SnCl_2$ to the hexahydropyridazine **38** (93T8605).



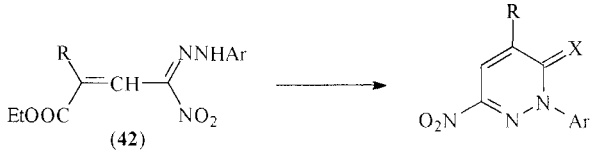
B. Diazo Coupling to Reactive Methylene Compounds

A great number of pyridazine syntheses involves this traditional reaction, followed by ring closure. Substituted enones **39** were transformed after coupling and hydrolysis into **40,** which gave with reactive methylene groups of compounds such as ethyl cyanoacetate, malonodinitrile, or diethyl malonate the corresponding pyridazines **41** (97S91). Similar syntheses were reported with coupling products of 1,3-diketones [91OPP645;



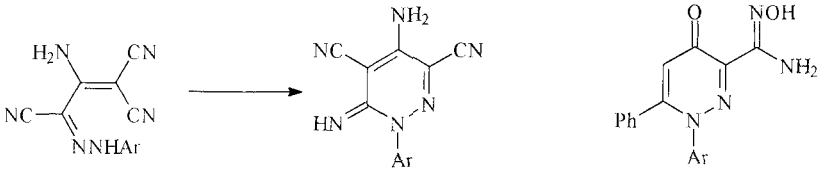
(39) (40) X = NH, O (41)

93JCR(S)358, 93OPP293; 94PS(88)147; 97SC2419], 1,3-keto esters [89JHC169; 90CCC2977; 96JCR(S)434] or 1,3-cyanoketones [89T3597; 90ZN(B)389]. Compounds **42,** prepared from potassium salts of cyano or ethoxycarbonyl substituted 1-propenes and aryldiazonium tetrafluoroborates, were transformed into **43.** If the starting compound was ethyl cyanoacetate besides the main product (X=O), the imino compound (X=NH) was obtained as a result of the attack of the NH group to the cyano group (91ZOR1105).



(42) R = CN, COOEt X = O, NH (43)

A number of hydrazones, resulting from coupling of arenediazonium salts to unsaturated crotononitriles, afforded after cyclization pyridazines, for example **44** (89AP535, 89JPR375; 90BCJ652, 90CCC734, 90LA293; 91AP853; 92PHA418; 93BCJ1722; 95HAC281). In a similar manner, arylhydrazones of cinnamoylacetonitrile, when treated with hydroxylamine, gave **45** (94CCC186). From 3-oxo-2-phenylhydrazonobutyronitriles and reactive methylene compounds various substituted pyridazines could be prepared. The reaction with ethyl cyanoacetate at 110°C gave **46,** whereas at 150–160°C **47** was obtained. In the last case the reaction between the methylene group and the cyano group takes place (89G95). A similar case represents the reaction with malononitrile (92CCC1758).



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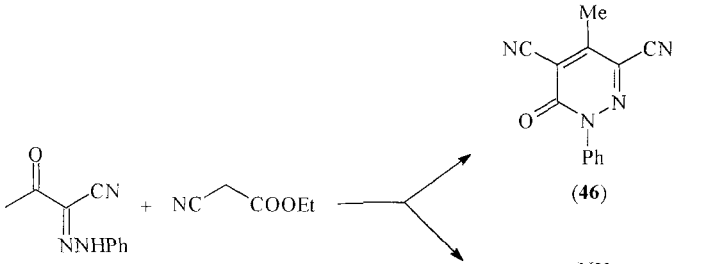
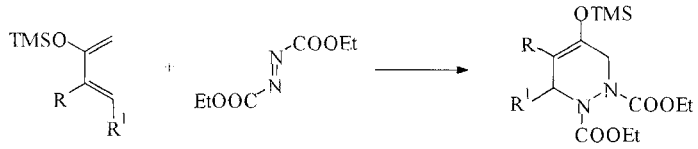


(46) (47)

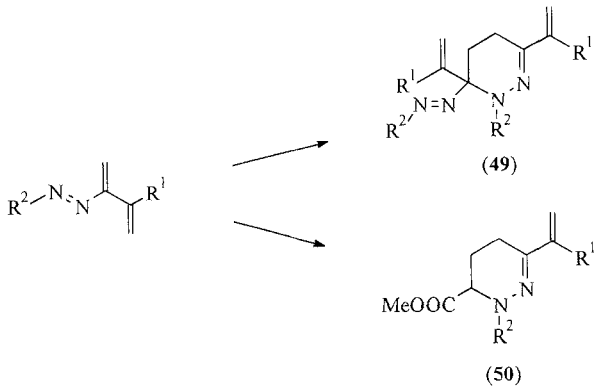
C. Cycloadditions

There are some examples of cycloadditions of dienes to aza compounds as, for example, reactions of substituted trimethylsilyloxybutadienes with diethyl azodicarboxylate to give **48** (90JHC2125; 91KGS783; 94JHC967). The trimethylsilyloxy substituent in **48** can be transformed into an amino or substituted amino group to give the corresponding aminopyridazines. Both reactive groups can be in the same molecule and 1-alkyl-2-(1-methylene-2-



(48)

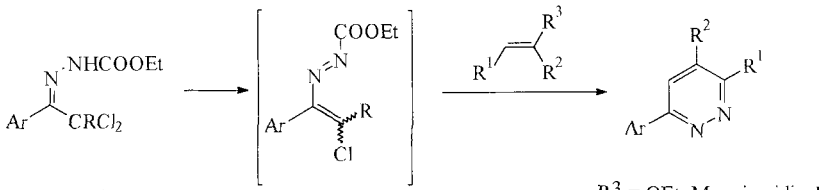
propenyl)diazenes dimerize rapidly at room temperature in a regioselective manner to give **49.** In the presence of methyl acrylate **49** is again formed together with **50** in moderate yield (92TL7331).



(49)

(50)

Dichlorodiazenes, generated from hydrazones of dichloro or trichloro analogs of acetophenone with Hünig's base, reacted with electron-rich alkenes to give a diastereoisomeric mixture of tetrahydropyridazines which were subsequently aromatized with a base to **51.** In some cases also pyrroles were formed and the ratio of both types of compounds depends on the alkene substituent (95TL5703; 96JOC8921, 96TL1351). Representing a stable azo compound, 4-phenyl- 1,2,4-triazoline-3,5-dione (PTAD) was employed to produce pyridazine derivatives via cycloadducts (88SC2225; 98JOC4912). In this manner bis-4,5-adamantylpyridazine was prepared (98JOC4912). Pyridazine-3,4-dicarboxylic acid (or its diester) could be obtained in moderate yield using a hetero Diels–Alder reaction between a diazadiene and ethyl vinyl ether. The resulting tetrahydropyridazine derivative was oxidized in the usual manner and saponified (90JHC579) and similarly 3-methylpyridazine-4-carboxylate could be prepared (91JHC1043). Alkenyl hydrazides were cyclized with phenylselenyl sulfate

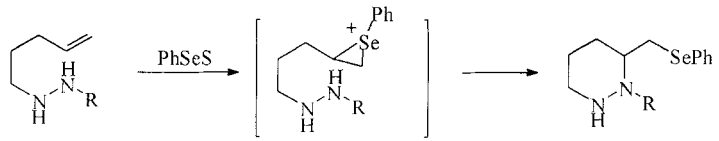


R = H, Cl

R^3 = OEt, Mo, piperidinyl

(51)

via the intermediates **52** to hexahydropyridazines **53** together with pyrrolidines as minor products. Compounds **53** were partially oxidized during the workup into tetrahydropyridazines (97T10591).

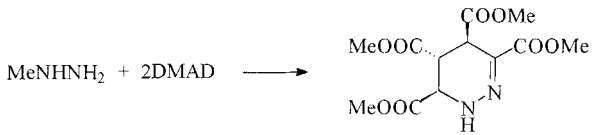


(52) (53)

Reactions of ene-hydrazines with DMAD were investigated under various reaction conditions. In aqueous MeOH at −8°C the major products were tetrahydropyridazines **54.** Purification by column chromatography on silicagel resulted in the inversion of the configuration of the 4-methoxycarbonyl group. In a one-pot reaction of methylhydrazine with 2 equivalents of DMAD in

(54)

aqueous MeOH at room temperature the isomeric **55** was obtained as the major product (88CB2007). In a simple new method 4-(*o*-hydroxyphenyl)-3(2*H*)-pyridazinones can be prepared by 1,3-dipolar cycloaddition of the *in situ* prepared diarylnitrilimines and 3-arylidene-2(3*H*)-benzofuranones. From both isomers, *E* or *Z*, the same pyridazine **56** is obtained (97S1495).



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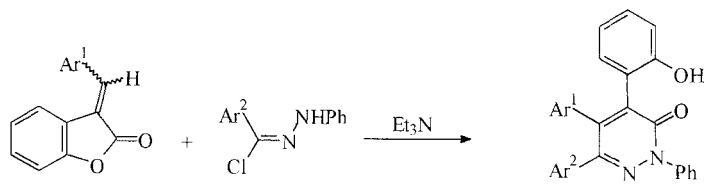
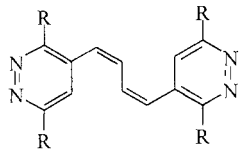


(56)

A substantial number of pyridazine preparations is based on the well-elaborated cycloaddition process, which employs tetrazines or triazines as synthons in the inverse-type Diels–Alder reactions. 3-Phenyl-1,2,4,5-tetrazine reacted with 1, 1-donor- and acceptor-substituted ethylenes as dienophiles in a regiospecific manner. The *ortho*-regioisomer was formed in >99.9% yield (90TL6855). When a mixture of 3,6-diaryl-1,2,4,5-tetrazine, elemental sulfur, and triethylamine was refluxed in toluene with addition of 1,4-dihydrotetrazines 3,6-diarylpyridazines were obtained. The formation of the latter was explained by the intermediate formation of diethylaminoethylene molecules from triethylamine. The ratio of products varied and in the case of diphenyltetrazine 3,6-diphenylpyridazine was the only product (91ZOR1123; 97MI6). Pyridazines were obtained from tetrazines when using silyl enol ethers. The activating power of a Me_3SiO group is relatively low and is comparable to that of the MeO group. It was established that *trans*-dienophiles are more reactive than the *cis* forms by a factor of 1.35–10.7 (92TL8019). From 3-methoxy-6-methylthio-1,2,4,5-tetrazine and silyl enol ethers or cyanoalkyl enamines the corresponding 5-phenyl- or 5-cyanoalkyl-3-methoxy-6-methylthiopyridazines could be prepared (97TL3805). Pyridazines were prepared also from styrenes and the reaction kinetics were studied. The second-order rate constants for this reaction increase dramatically in water-rich and acidic media (96JOC2001). Other examples include the use of methyleneheterocycles to give spiro-substituted pyridazines (90KGS1244, 90KGS1691; 91KGS1545), the highly reactive 1,3-dimethyl 2-cyclopropylideneimidazolidine (89AG1288), an *N*-protected indole (97TL8611), bisdienophiles (from cyclooctatriene **57** was obtained) (97JPR623), or azolylbutadienes to give in most cases 4-*Z*-azolylvinyl-substituted pyridazines (95JOC4919; 96JOC4423). Also, solid-support-immobilized 1,2,4,5-tetrazines were used for reactions with various dienophiles (96TL8151).



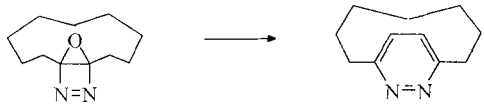
(57)

Extensive studies of preparation of 4-mono- and 4,5-disubstituted pyridazines from 1,2,4,5-tetrazines using donor-substituted alkenes, alkynes, ketene aminals, or styrenes were reported by Sauer. Pyridazine itself can be prepared from 1,2,4,5-tetrazine and acetylene (27% yield), ethyl vinyl ether (78% yield), methyl vinyl sulfide (76% yield), or *N*,*N*-dimethylvinyl-

amine (61% yield). From kinetic measurements rate constants were determined and rules were established concerning the influence of steric and electronic effects of substituents in the dienophile (98MI1). A checked procedure for the synthesis of dimethyl 4-phenylpyridazine-3,6-dicarboxylate was published (92OS79). Silyl-, stannyl-, or germanylalkynes were used to prepare the corresponding 4-trimethylsilyl-, trimethylgermanyl-, or tributyltin-pyridazines (91H1387; 97TL5791; 98T4297, 98TL5873). Protected acetylenic sugars were used for the preparation of 4-(β-D-ribofuranosyl)pyridazines (94AP365). Compounds having two acetylenic or ethylenic groups separated by space linkers were also used for the preparation of the corresponding pyridazines [96JCR(S)448].

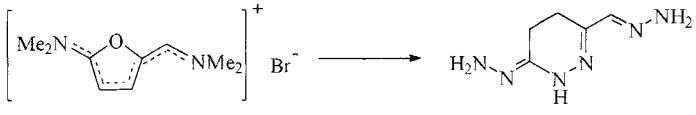
D. From Other Heterocycles

Pyridazines have been prepared from a variety of other heterocyclic systems and in most cases these transformations were specific. The 3(*S*), 4(*S*) **36,** a constituent of the antibiotic antitumor luzopeptin A, was prepared in a multistep synthesis from malonaldehyde dimethyl acetal in 32% overall yield. In the last step a highly regiospecific nucleophilic ring opening of the glycidic acid (oxirane derivative) took place (89JOC3260). In another example, *cis,trans*-1,3-cycloundecadiene was transformed in five steps in low yield into **59.** In the last step the epoxide **58** was treated with excess of LDA (89TL4649).



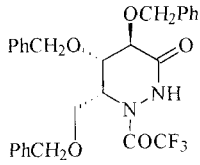
(58) (59)

Several methods for the preparation of pyridazines from furan derivatives were already known. However, a new method has been developed by using furan vinamidinium salts **60** as starting material. They react with hydrazine at position 5, thereafter they add to the enamine system with subsequent ring opening and ring closure to give **61** (88CCC1297).



(60) (61)

From 2,5-dimethoxytetrahydrofuran and hydrazines *N*-substituted 1,4,5,6-tetrahydropyridazines were prepared (97T3707) and from 2,5-diacetoxymethylfuran 3,6-bis(hydroxymethyl)pyridazine was obtained (96JHC2059). 2-Furanones and 3-furanones as such or with either a methylene or hydrazone neighboring group were used to prepare 3(2*H*)- or 4(1*H*)-pyridazinones (88JOC5704; 90H1967, 90KGS1138, 90ZOR2022; 98T6553). In connection with the synthetic approaches toward the glidobactin antibiotics the pyridazine derivative **62** was prepared from a furanone derivative in several steps (91T6251).



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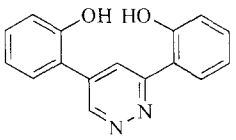
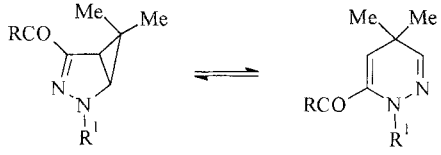


(63)

There are some examples when *N*-aminopyrroles were transformed into pyridazines either in boiling toluene (94ZOR1433) or after treatment with a Grignard reagent [96ZN(B)1334; 98S1627].

From phenylazo-substituted thiophenes pyridazines were formed with hot alkali and the azo group is incorporated in the ring (88M985). With bulky groups (adamantyl, *tert*-butyl and neopentyl) at positions 4 and 5 substituted pyridazines were prepared by reacting the corresponding thiophenes with PTAD, followed by treatment with alkali and air oxidation and nitrogen extrusion [89H(29)1241; 90JA5654; 91PS(59)243; 94TL2709].

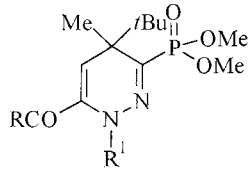
Pyridazines can be prepared from 4,5-dihydroisoxazoles. By reductive N–O bond cleavage the resulting α-hydroxy-γ-keto esters gave pyridazines with hydrazine. The reaction has been extended to the synthesis of a 3(2*H*)-pyridazinone 6-D-β-ribofuranosyl derivative (*C*-nucleoside) (94MI3, 94S1158). An unusual synthesis of a pyridazine was reported starting from 3-methyl-1,2-benzisoxazole after treatment with LDA or *sec*-butyllithium. Among other products a dihydropyridazine and its aromatic analog **63** were isolated. The mechanism of this transformation was delineated and the pyridazine ring nitrogens are generated from two isoxazole ring nitrogens (89JOC4970). The rearrangement of 3-acetyl-4-aryl-2-pyrazolinones into 3-methyl-5-aryl-4(1*H*)-pyridazinones under various reaction conditions was investigated [95IJC(B)342]. The bicyclic pyrazoles **64,** obtained from (1-diazo-2-oxoalkyl)silanes and 3,3-dimethyl-1-cyclopropene, exist in solution in equilibrium with the pyridazines **65.** In the absence of solvent either a mixture of **64** and **65** or only **65** if R=aryl was obtained. The above



$R^1 = Si(iPr)_3$

(64) (65)

isomerization is slow on the NMR time scale, even at higher temperatures. If the cyclopropane ring carries an electron-withdrawing group [like $PO(OMe)_2$ or COOMe] the pyridazine **66** is the sole product (92CB1227; 98JOC9880) β-Keto esters reacted with hydrazones in absence of solvent and under microwave irradiation to give pyridazinones **68** as thermodynamically controlled products. These are also formed from the kinetically controlled product **67** if it is submitted to focused microwave irradiation in the presence of piperidine (96T5819). Pyridazines were obtained also by ring opening of condensed five- and six-membered heterocycles such as isoxazolo[4,5-*d*]pyridazines (90JHC927), isoxazolo[3,4-*d*]pyridazines (reductive or oxidative ring cleavage of the isoxazole ring) [89H(29)1595, 89S213; 91FA873, 91H1173], or 1,2,5-oxadiazolo[3,4-*d*]pyridazines (reduction to give 4,5-diaminopyridazines) (92JHC87, 92LA547). The 3,6-diamino analog could be prepared from 6-azidotetrazolo[1,5-*b*]pyridazine after treatment with either phosphanes or trimethyl phosphite (91LA1225). The bicyclic compound **69** is cleaved with potassium *tert*-butoxide at room tem-



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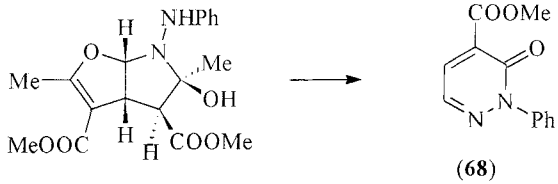
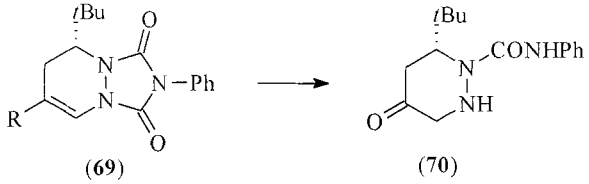


(67) (68)

perature into **70** without racemization with 91% ee (94S66). Derivatives of **69** (prepared by cycloaddition from 2,4-pentanedienol and PTAD) were used to synthesize glycosidase inhibitors 1-azafagonine [(3,4-*trans*-4,5-*trans*)-4,5-dihydroxy-3-hydroxymethylhexahydropyridazine] and its 5-fluoro analog (97MI3, 97T9357).



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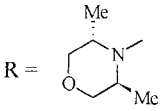
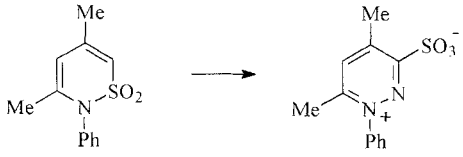


There are some reports of transformations of six-membered heterocycles into pyridazine derivatives. Traces of pyridazine were detected when 1,2,3-triazine was submitted to neat thermolysis at 130°C (92H1183). 1,1-Dioxo-1,2-thiazines **71** are transformed upon nitrozation into the mesoionic pyridazinium salts **72,** but the reaction can also proceed further in such a manner that the 6-methyl group is transformed into a hydroxyiminomethylene group [94AX(C)1150; 95JPR104]. Arylhydrazines gave with **73** reduced pyridazinones **74** (93H219) and 1,2,4-triazines **75** reacted with



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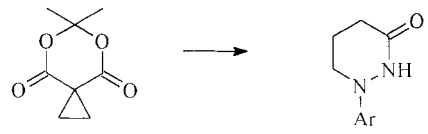

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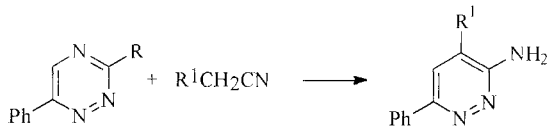
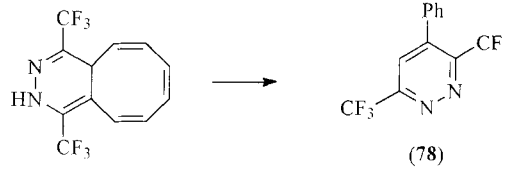


(75) (76)

cyanomethyl compounds in the presence of potassium *tert*-butoxide to give **76.** A ring-opening mechanism was proposed which was substantiated by the isolation of an acyclic intermediate (96TL5795). 2,7-Dihydro-1,4,5-thiadiazepines are thermally decomposed into pyridazines with evolution of H_2S (89BCJ2608) and when **77** was heated in nitrobenzene at 211°C and in the presence of CuI/O_2 it was transformed into **78** (91TL5949). In the case of a pyrimido[1,2-*b*]pyridazine, upon heating with morpholine the pyrimidine part was opened to give **79** with *E*-configuration of the side-chain (88JHC1535).



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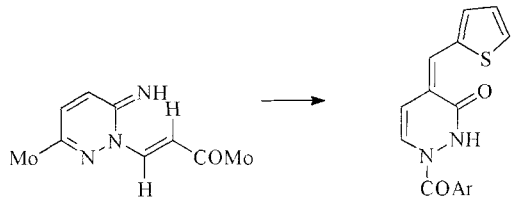


(79) (80)

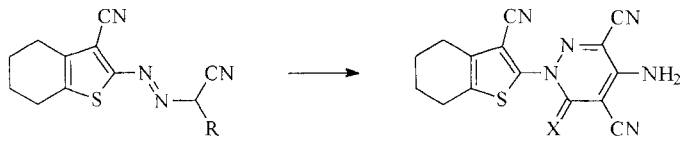
E. Pyridazines Substituted with Another Heterocyclic Ring

A substantial number of pyridazines, substituted with another heterocyclic ring, have been prepared since the late 1980s. It was therefore decided to summarize their preparation in a special section.

4-(4-Pyridazinyl)-3-substituted β-lactams were prepared either from 4-pyridazinecarbaldehyde-derived imines and lithium enolates of α-

substituted acetates in reasonable yields (96JHC1731) or from acetylenic azetidinones and 3,6-bis(methylthio)-1,2,4,5-tetrazine in a cycloaddition reaction (97TL5913).

5-(Furyl-2)- or 5-(thienyl-2-)-substituted 1,4-dihydropyridazines could be prepared from 2-alkoxycarbonyl-1,3-pentanediones (activated methine compounds) and 1-aminocarbonyl-1,2-diaza-1,3-butadienes (98JOC9880). One example of a 5,6-difur-2′-yl-3-(2*H*)-pyridazinone is prepared from difuryl-1,2-diketone, ethyl cyanoacetate, and hydrazine [94PS(86)203]. From 3,6-dichloropyridazine and *N*-pyrrolylmagnesium bromide, 3-chloro-6-(2-pyrrolyl)pyridazine was prepared; attempted disubstitution failed (98T9519). A substituted 2-(pyrrol-4-yl)-1,4-keto acid served as starting material for 4-heteroaryl-substituted pyridazinone (90MI3). The same approach was used for the analogous 3-indolyl compounds (93RRC1223). The classic Fischer indole synthesis was applied for the preparation of 6-(1*H*-indol-5-yl)-3(2*H*)-pyridazinones(90JMC2870) and with an indole ring at position 4 substituted pyridazines from 2- or 3-vinylindoles by either cycloaddition with a tetrazine (88TL3927; 89HCA65) or in a related Nef reaction with ethyl acetoacetate and hydrazine [93IJC(B)662]. A number of thienyl- or benzothienyl-substituted pyridazines was prepared as follows (the first number in parenthesis refers to the heteroaryl ring position and the second to the pyridazine ring position through which both rings are linked). As starting material 1,4-keto acids or 1,4-diketones substituted with a thiophene ring were used to give the corresponding compounds: 2–3 bonds (91AP455), 2–4 bonds [96IJC(B)1097], 2–3 or 2–5 bonds [95JCR(S)306], or 2–3 or 3–3 bonds (89JMC528). Compounds **80** were prepared from the corresponding thienylidene derivatives of diaroylhydrazines (93CCC1925). In a new approach 2- or 3-tris(*n*-butyl) stannylthiophene was coupled with 3-halopyridazines (3–3 or 2–3 bonds) in a palladium-catalyzed reaction [95JCR(S)402, 95JOC748]. Benzo[*b*]thiophenylpyridazines (2–1 bonds) **82** were obtained from the 3-cyano or ethoxycarbonyl compounds **81** and ethyl cyanoacetate or other compounds with a reactive methylene group [95JCR(S)434; 96JCR(S)440].



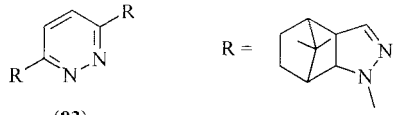
R = CN, COOEt

(81)

X = O, NH, S

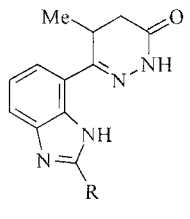
(82)

Substituted pyridazines with a pyrazole ring were prepared either from hydrazinopyridazines and 1,3-keto esters (1–3 bonds) (91RRC657; 93JHC865; 97JHC389) or from a with γ-keto-acid-substituted pyrazole and hydrazines (4–4 bonds) [91BCJ2032, 91MI3; 92MI3, 92MI4; 93BCJ477; 94M1437; 95IJC(B)57, 95M1265]. In a special case, a camphor-derived pyrazole was treated with 3,6-dichloropyridazine or 3-chloro-6-phenylpyridazine to give **83** or the phenyl analog (95AJC1549).

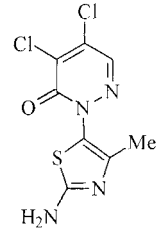


(**83**)

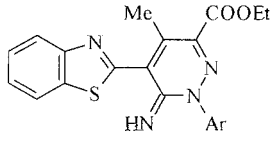
An imidazole ring can be attached to a pyridazine ring in several ways. In one approach 4,5-dicyano-2-diazo-2*H*-imidazole reacted with a 1,3-diene whereupon the pyridazine ring is formed (2–1 bond) [90JCS(P2)1943] and in the other protected 5-tris(*n*-butyl)stannylimidazole was reacted with methyl 3-chloropyridazine-6-carboxylate with formation of a 5–3 bond (95JMC2925). Benzimidazolo-pyridazinones **84** were prepared from the corresponding benzothiadiazolo analog by ring opening and desulfurization with Raney-nickel, followed by cyclization of the diamine (93MI4, 93MI5). A thiazole ring was formed in the usual manner from a bromoketone and thiourea to give **85** (91JHC1235) and **86** was obtained from 2-cyanomethylbenzothiazole and an arylhydrazone of ethyl acetoacetate (88AP509). 6-Benzothiazolyl, benzothienyl, and other heteroarylpyridazines were prepared by standard method from the appropriate γ-keto esters and hydrazine (91CPB352). 1,2,4-Triazolylpyridazines (3–4 bond) were obtained from 3-amino-4-cyanopyridazine. The cyano group was transformed into an amidrazone group and DMF–DMA was used for cyclization. Two products, in yields of 20 and 43%, respectively, were obtained but no unambiguous structural assignment could be made (91JHC1441). Ring-



(**84**)

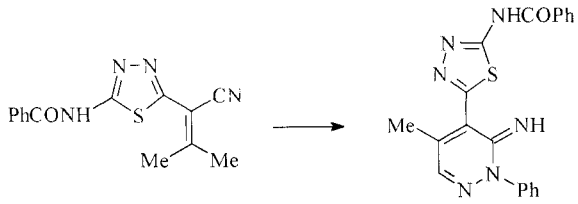


(**85**)



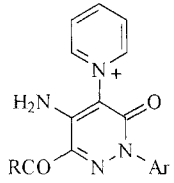
(**86**)

substituted pyridazine **88** with a 1,3,4-thiadiazole was prepared in moderate yield from **87** after the methyl group reacted with benzenediazonium chloride [95PS(102)51].



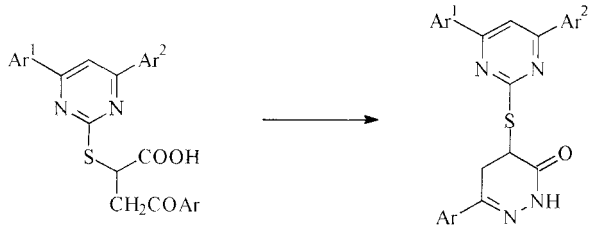
(87) (88)

Among six-membered heterocycles compound **89** was obtained when *N*-chloroacetyl derivatives of arylhydrazonoacetamides were treated with pyridines and the initially quaternization of pyridines is followed by a Thorpe–Ziegler cyclization. If the pyridine ring is opened with hydrazine hydrate,4,5-diaminopyridazine derivatives are formed (95M341). From **154** after treatment with cyanoacetamide 3-cyano-5-(4-pyridazinyl)-2(1*H*)-pyridone was obtained and in a similar transformation from **155** the 6-methyl analog was formed (89PHA598). 4-Acetylpyridine, when alkylated with diethyl mesoxalate at the methyl group, afforded a substituted 1,4-keto ester, which cyclized into a 6-(4-pyridinyl)pyridazinone derivative (90H2163). Two units of 3,6-bis(2-pyridinyl)pyridazine were prepared space separated as chelating agent from dipyridyltetrazine by cycloaddition (94TL6745). 4-Tributylstannylpyridazine was used to react with 2-halopyridine (or 5-halopyrimidine) to give the corresponding 4-heteroarylpyridazines (97TL5791).

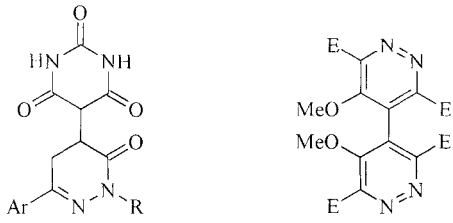


(89)

Pyrimidinylpyridazines were prepared either from **90** to give **91** (96RRC109) or when barbituric acid was reacted with a benzoylacrylic acid and the adducts were thereafter cyclized to **92** (94MI2).



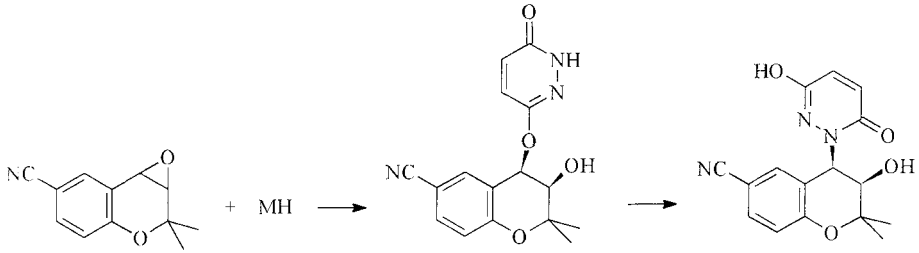
(90) (91)



(92) (93)

A bis-pyridazinyl system **93** was prepared from 1,1,4,4-tetramethoxy-1,3-butadiene and 3,6-dicarbomethoxy-1,2,4,5-tetrazine (93JA8457) and piperazinylpyridazine derivatives (3–1 bond) were prepared from the corresponding 3-chloropyridazines (98JMC311).

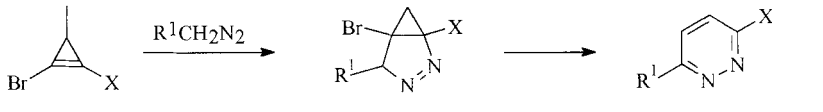
A benzopyran-substituted pyridazine **96** was prepared by reacting the epoxide **94** with maleic hydrazide after heating the intermediate product **95** with NaH in DMSO (90JMC2579). For a related compound, coupling of a diazonium salt with an activated methylene group was applied (92G41). The classic condensation method of heteroarylsubstituted 1,4-keto esters or halo compounds with hydrazine was applied for the preparation of quinolylpyridazines(7–1 and 6–6 bonds) [88JHC1543; 89H(28)1085], quinazolylpyridazines (7–6 bond) (96JMC297), or 1,4-benzoxazinylpyridazines (6–6 bond) [89IJC(B)882; 90JMC380; 91SC271].



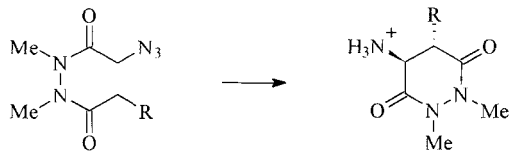
(94) (95) (96)

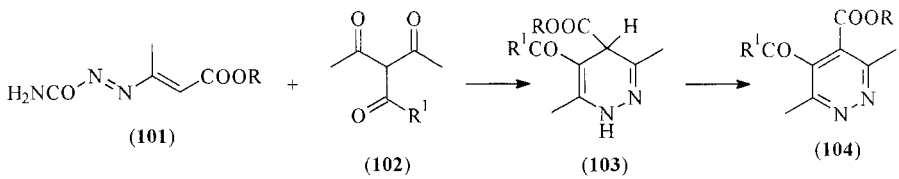
F. Miscellaneous Syntheses

There are several specific synthetic approaches used to prepare particular pyridazine derivatives. 3-Amino-4,5-dicyanopyridazines were formed [95PS(101)189, 95PS(106)167] from *S*-methyldithiocarbazate or thiosemicarbazide via an initial intermolecular charge transfer complex. Sterically hindered cyclopropenyldiazomethanes were transformed at room temperature or upon heating into sterically crowded pyridazines (with several *tert*-butyl, *iso*-propyl, adamantyl groups) (91AG1495, 91TL57; 95LA169, 95LA173). 1-Bromo- and 1,2-dibromocyclopropenes react with diazoalkanes to give **97** and these compounds are rearranged in solution into **98** (98T12897).

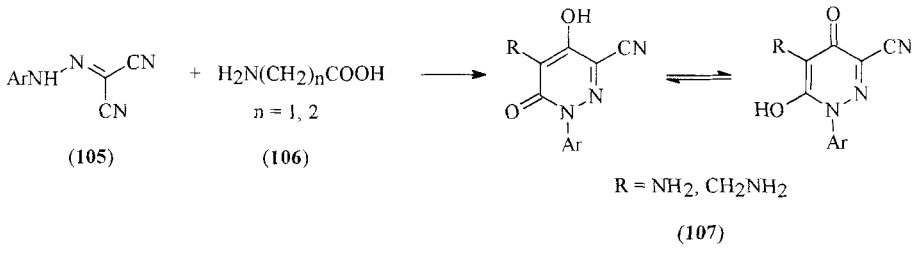


Azide-substituted hydrazides **99** (R=Me, Ph) were transformed into bis (enolsilanes) with TMSOTf followed by C–C bond formation to give **100** (*trans:cis* ratio > 20 : 1) (97JOC5680). Azoalkenes **101** react smoothly at room temperature with β-tricarbonyl compounds **102** (R=Me, OMe) in the presence of NaH to give **103.** The ring-closing process is accompanied by the cleavage of the N_1-substituent and upon aromatization **104** was ob-

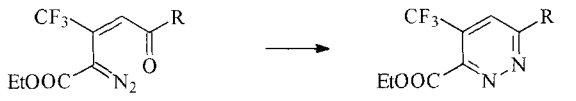




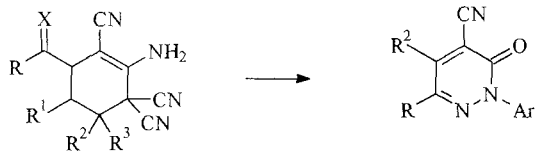
tained (97SL1361). Arylhydrazones of mesoxalonitriles **105** react with the methylene group of either glycine **106** (n=1) or β-alanine **106** (n=2) to give **107** (92PHA792). In a special synthetic route vinyldiazomethanes **108** were treated with Ph_3P at room temperature to give **109** in moderate to good yields (95S920). Alkylidenemalononitrile dimers **110** (X=H_2), when coupled with diazonium salts, afforded the products **110** (X=NNHAr) and these were cyclized in the presence of piperidine in ethanol to pyridazines **111** (93AP39). In a multistep synthesis enantiomerically pure hexahydropyridazine-3-carboxylic acid **113** was prepared. In the cyclization step the glutamic-acid-derived acetal **112** was cyclized with HCl to the tetrahydropyridazine carboxylate, which was then reduced with $NaBH_3CN$ to **113**



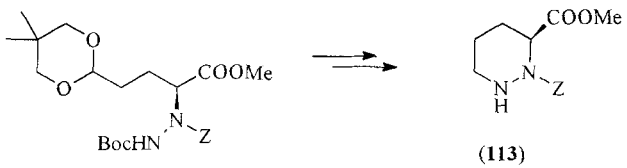
(105) (106) R = NH_2, CH_2NH_2 (107)



(108) R = OEt, *t*Bu, Me (109)

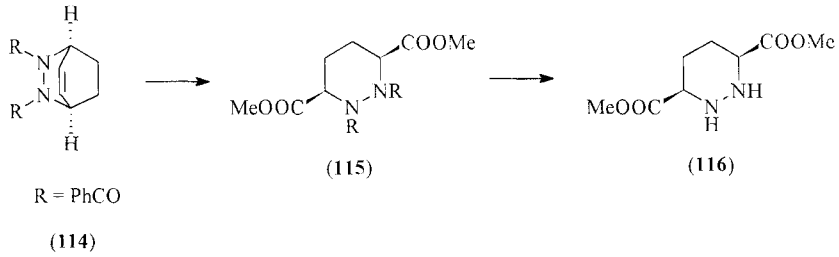


(110) (111)



(112) (113)

(96S223). *Cis*-3,6-piperidazinedicarboxylic acid **116** could be prepared from the adduct **114** which was oxidized with ruthenium tetroxide at 0°C to give, after esterification, the ester **115**. Hydrolysis of the latter afforded **116** (95CPB535).



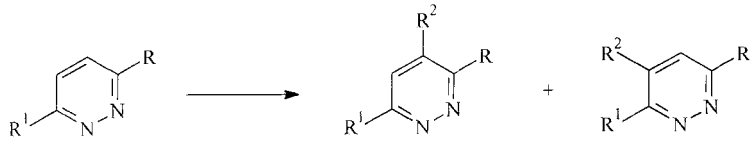
IV. Transformations of Pyridazines

A. Reactions at the Ring-Carbon Atoms

Introduction of substituents into pyridazines has been widely investigated and as generally known, the π-electron deficiency of the ring facilitates nucleophilic reactions. A review on nucleophilic and electrophilic substitutions at the pyridazine nucleus appeared (94MI4). Since the late 1980s metalation followed by the introduction of various substituents has been thoroughly investigated. Reviews dealing with the metalation of diazines also include pyridazines [94H(37)2149; 95H(40)1055]. A variety of organolithium reagents was employed and it appears that LDA and LTMP (lithium 2,2,6,6-tetramethylpiperidine) are preferred.

Pyridazine was lithiated with excess of LTMP and after reaction with various electrophilic reagents (RCHO, Ph_2CO, PhSSPh, I_2) mixtures of 3-mono- and 3,6-disubstituted pyridazines were obtained [new substituents: RCH(OH), $Ph_2C(OH)$, PhS, I]. (95JOC3781). Using this procedure *N*-protected 4-aminopyridazines afforded newly substituted compounds at position 5. Pyridazine substituted with an oxazoline ring at position 4 when treated with LTMP and then with acetaldehyde or benzaldehyde afforded a mixture of 3-alkylated (22–24%), 5-alkylated (8%), and 6-alkylated (3–7%) products (95JHC841). Pyridazines substituted with the same substituent at positions 3 and 6 (dichloro, dimethoxy) were transformed into 4-substituted derivatives (90JHC1377, 90JOC3410; 98SL762). The situation became more complicated with different substituents at positions 3 and 6 and sometimes a mixture of regioisomers was obtained. In the

case of **117a** and after quenching with aldehydes the isomer **118** [R^2=RCH(OH)] was predominant (93T599) and from **117b** the major isomer was **119** [R^2=RCH(OH), Me, I] (98JHC429). From **117f** and using MeI **118** (R^2=Me) could be prepared (93BSF488). From **117d** and TMSCl the trimethylsilyl derivative **118** (R^2=$SiMe_3$) was obtained (95JHC1057) and similar transformations were observed with tosyl azide to give **118** (R^2=N_3) (96MI3, 96S838). In an exhaustive investigation of metalation of **117d** with alkylamides, numerous factors influencing the formation of regioisomers were studied (various nucleophiles, nature and amount of alkylamide, variation of time and temperature, and influence of solvent and concentration). Very good regioselectivity was observed when using some hindered bases and in such cases the ratio of **119** to **118** was from 91/9 to 99/1 (96T10417). In another study 3,6-disubstituted pyridazines were metalated with *sec*-BuLi and afforded **119** (R^2=*sec*-Bu), accompanied with a low amount of the 4,5-dihydro product and traces of **118** (R^2=*sec*-Bu). Less reactive PhLi and vinyllithium did not react with 3,6-dichloropyridazine, but with MeLi a coupling product, structurally related to **93,** was obtained (98SL762). Lithiation of **117c** followed by reaction with acetaldehyde resulted exclusively in the formation of **118** [R^2=MeCH(OH)], but with 3-methoxy-6-phenylsulfinylpyridazine the same reaction with various electrophiles afforded only 5-substituted products **119** (97JHC621).

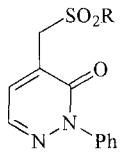


(117) (118) (119)

	R	R^1
a:	H or Cl	NHCO-*t*Bu
b:	OMe	SO_n-*t*Bu (n = 1,2)
c:	OMe	SPh
d:	OMe	Cl
e:	Ph	Cl
f:	Ph	OMe

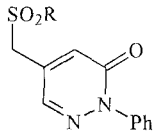
Various pyridazines, their 3-oxo or 3,6-dioxo analogs, readily undergo vicarious nucleophilic substitution (VNS) with the carbanion of chloromethyl *p*-tolyl sulfone. 2-Phenyl-3(2*H*)-pyridazinone, of a higher reactivity as an

electrophile than pyridazine, gives a mixture of compounds **120** (26%), **121** (12%), and **122** (15%). Compound **122** resulted via intramolecular S_N2 reaction in the intermediate σ-adduct (92TL4787). Vicarious nucleophilic substitution takes place also with pyridazinium *N*-dicyanomethylides and the phenyl or *p*-tolylsulfonylmethyl groups are introduced regiospecifically at position 4 [95JCS(CC)2067; 98JCS(P1)1637].

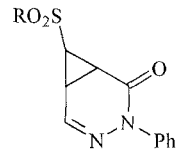


R = *p*-tolyl

(120)

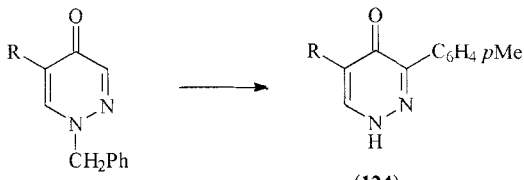


(121)



(122)

With a tertiary amino group at position 5 substituted 2-methyl-3(2*H*)-pyridazinones were readily formylated with the Vilsmeier–Haack reagent to give 4-formyl derivatives [94H(37)171]. 6-Substituted 4,5-dihydro-3(2*H*)-pyridazinones can be transformed under a base-catalyzed reaction with aromatic aldehydes to aromatic 4-arylmethyl derivatives (88ACH631; 89MI3; 90ACH829). 1,2-Diprotected 1,2,3,6- and 1,2,3,4-tetrahydropyridazines were hydroformylated in the presence of various metal complexes to give the 3- and 4-aldehydes with simultaneous hydrogenation of the pyridazine ring (93JOM229). In the course of the preparation of a pyridazine by debenzylation of **123,** up to 20% of **124** was obtained [89H(29)1309].



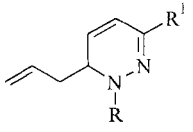
R = ArCO

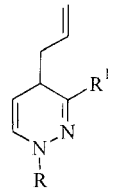
(123)

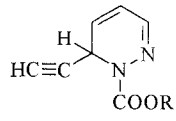
(124)

Alkylation of pyridazines was investigated with the use of organotin reagents. Pyridazine or its 3-substituted derivatives react in the presence of chloroformate to give 1,6- and 1,4-dihydro adducts **125** and **126** in good yields. From pyridazine, **125** and **126** were obtained ina ratio of 1:4.5 if ethyl

chloroformate was used, whereas in all other cases the 1,6-dihydro isomer prevailed. The adducts were obtained as a mixture of two to four conformational isomers [94CPB1768, 94H(37)709]. Pyridazine, when ethynylated with bis(tributylstannyl) acetylene in the presence of alkyl chloroformate, afforded **127** (94SL557, 94T13089).



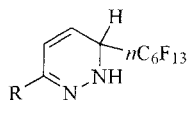


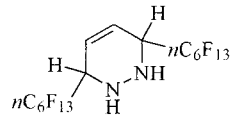


R = COOEt, Me
R^1 = H, Me, Ph, COOMe

(125) (126) (127)

Perfluoroalkylation of pyridazine and its 3-*n*-C_6F_{13} derivative with *n*-$C_6F_{13}I$ in the presence of BF_3-etherate gave, in the case of pyridazine, a mixture of 3-substituted and 3,6-disubstituted adducts **128** (R=H) and **129**; the 3-fluoroalkylated derivative gave only the mono adduct **128** (R=*n*-C_6F_{13})(91T6231). Pyridazine reacted also with silyl enol ethers in the presence of alkyl chloroformate to give various proportions of 1,4- and 1,6-dihydro adducts. Unsubstituted enolates gave 1,6-adducts exclusively and silyl enol ethers with two substituents at vicinal position gave 1,4-adducts as the sole product [97H(46)83].

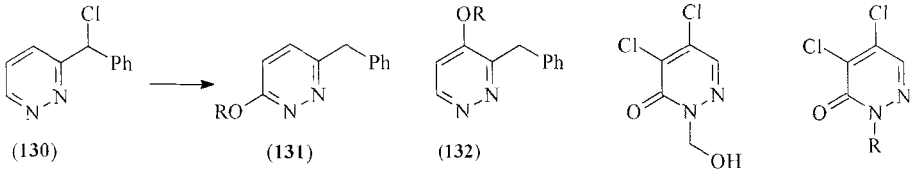




(128) (129)

Halogenation of *N*-arylpyridazines with different reagents was investigated. With Br_2 in ethanol monobromination occurred and monochlorination was achieved with sulfuryl chloride in dioxane. Dichlorination occurred with excess of chlorine gas in dichloromethane (90M565). Pyridazine showed a surprisingly high dipolarophilic activity toward benzonitrile oxide at the most polar C=N bond. The cycloadduct formed upon standing in solvents undergoes autooxidation in the presence of air and in

1–2 weeks 3(2*H*)-pyridazinone is formed in 90% yield (95T11855; 96T6421). An alkoxy group can be introduced into the pyridazine ring by telesubstitution of the chlorine atom in **130** to give **131** or **132.** An electron-donating group at position 6 prevents this transformation (92LA19). 6-Substituted 3(2*H*)-pyridazinones can be aminated straightforwardly with boiling hydrazine hydrate exclusively at position 4 in moderate to excellent yields. Unsubstituted 3(2*H*)-pyridazinone afforded a mixture of the 4-amino (24%) and 5-amino compounds (14%). At higher temperatures (180–190°C in ethylene glycol), the 6-substituted derivatives gave in low yield a mixture of the 4-amino derivative and 3-hydrazino-6-arylpyridazine [89H(29)1077]. In connection with other heteroaromatics, amination of 4-nitropyridazines was reviewed (93ACS95).



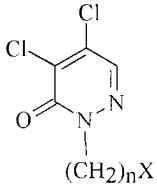
(130) (131) (132) (133) (134)

B. Reactions at the Ring-Nitrogen Atoms

N-Alkylation or acylation of 3(2*H*)-pyridazinones by standard procedures afforded derivatives with unambiguous structure, whereas pyridazines can yield either N_1- or N_2-substituted products. Pyridazine-4-carboxamide, when alkylated with 5-iodovaleric acid or related acids, yielded a mixture of both N_1- and N_2-regioisomers in the ratio of 1:1.25 or 1:1. They were not separated (95AP307; 96PHA76). Alkylation of 3-(2-pyrrolyl)pyridazine afforded the N_1-alkylated product, as evidenced from X-ray analysis [96AX(C)1002].

Many 3(2*H*)-pyridazinones were *N*-alkylated in search for compounds of biological activity [88CPB1558; 89CPB2832, 89MI1, 89MI7; 91MI1; 92FA37; 94MI9; 95AF947; 96CPB980; 97BMC(5)655]. 2-Aminoalkyl-3(2*H*)-pyridazinones were prepared by *N*-alkylation with tertiary chloroalkylamines by three different methods (92MI7). 4,5-Dichloro- or 4,5-dibromo-6(1*H*)-pyridazinones were oxopropylated with chloroacetone at position 1, but 4,5-dichloromaleic hydrazide afforded a mixture of the 1-alkylated and 1,2-dialkylated products in 33 and 56% yields, respectively (97JHC1307). Compound **133** was transformed upon alkyla-

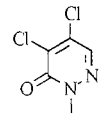
tion into **134,** obtainable also by direct alkylation of the 1-unsubstituted compound. Transformation of **133** to **134** proceeded via fragmentation of the retro-ene type in the first step followed by N_1-alkylation. Compound **133** reacted with α,ω-dibromoalkanes to give **135** and **136** or **137** (with 1,2-dibromoethane) as the main products (96JHC245, 96JHC615; 97JHC1135). 3-Aminopyridazines reacted with 3-methoxy-5-(chloromethyl)isoxazole or -isothiazole to give muscimol or thiomuscimole derivatives of pyridazine **138** (92JMC4092). In searching for endothelin receptor antagonists, pyridazinones or their 4,5-dihydro analogs were alkylated in the presence of cesium carbonate to give **139** and these were further functionalized at the carboxy group into acylsulfonamides [97BMC(7)275].



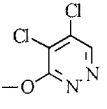
n = 1 - 6

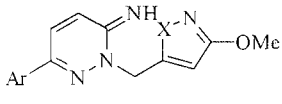
135 : X = Br

136 : X =



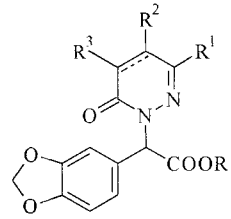
137 : X =





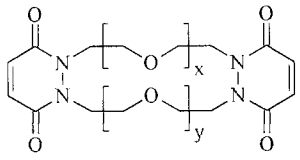
X = O, S

(138)



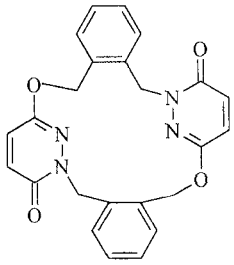
(139)

Pyridazine-3,6-dione has been alkylated at both nitrogens. Side-chains were introduced which in the last step allowed the formation of crown ethers **140** (97KGS1693). Pyridazine-based crown ethers were also obtained from commercially available crown ethers and 3,6-dichloropyridazine to give *N*-mono- or *N,N'*-diheteroarylated products [92JOC542; 93MI2; 95JCS(P1)2497]. The macrocycle **141** was prepared from maleic hydrazide and α,α'-dibromo-*o*-xylene (93ZOR911).

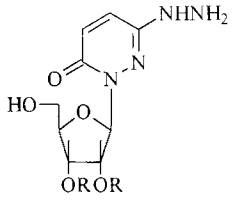


x = 1, 2, 3
y = 1, 2

(140)

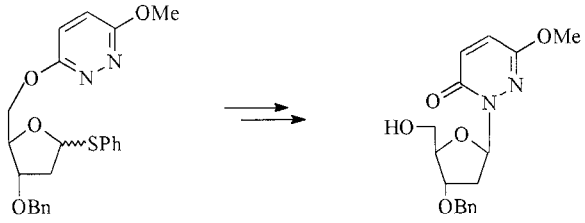


(141)



(142)

From 3-hydrazino-6(1*H*)-pyridazinone and protected β-D-ribofuranose the nucleoside **142** (R=Bz) was prepared and after deprotection with sodium methoxide **142** (R=H) was obtained (89MI6). The pyridazine analog of 2′-deoxycitidine was synthesized from 3-methoxy-6-chloropyridazine by intramolecular glycosylation of **143.** Compound **143** was treated with $Me_2S(SMe)BF_4$ and the oxonium intermediate was hydrolyzed to give the 2′-deoxynucleoside **144** (95MI4).



(143) (144)

Pyridazines were *N*-acylated with benzyl chloroformate [92JCS(P1)409], chloroacetic anhydride (93JOC633), sulfonyl chloride (93FA1427), and isocyanates (95ZOB37). 1-Aminopyridazinium nitrate was prepared from

pyridazine with hydroxylamine-*O*-sulfonic acid and barium nitrate in the presence of barium oxide in 34% yield (92JOC1585) and 3,6-dimethylpyridazine was *N*-aminated with *O*-(hydroxylamino) mesitylenesulfonate (92LA777). A series of substituted pyridazine *N*-oxides was prepared with peroxyacetic acid. In the case of 3-methyl-4-phenylpyridazine two isomeric *N*-oxides were obtained in a ratio of about 1:1. From 3-methyl-4-aryl-6-chloropyridazines only the 2-oxides were formed (96FA683; 97FA67). Pyridazine *N*-oxide was formed (70%) together with *N*-(perfluorobutanoyl)pyridazinium-1-amide (20%) when pyridazine reacted with perfluoro(2-butyl-3-propyloxaziridine) at −60°C. Pyridazine behaved as a nucleophile and attacked the three-membered ring either at the oxygen or nitrogen atom of the three-membered ring [96JCS(P1)2517].

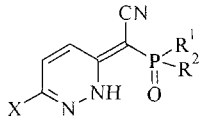
C. Reactions of Functional Groups

Substitution of halogen atom(s) of halopyridazines with amines, alcoholates, or thiolates still has been the dominant transformation of pyridazines since the late 1980s. Nevertheless, there are some novel reactions.

In the series of monohalopyridazines, 3-methoxy-6-phenylpyridazine, a precursor of the antidepressant minaprine, was prepared by arylation of 3-methoxy-6-chloropyridazine by Pd-catalyzed coupling with $PhB(OH)_2$ (93BSF488). 3-Fluoro-6-phenylpyridazine could be obtained in high yield from the chloro analog after treatment with PBu_4HF_2 or $PBu_4H_2F_3$ without solvent at 140°C (92H1507). In search for biologically active compounds pyridazines with an amino group containing a side-chain were prepared from various 3-chloropyridazines in the usual manner (88CPB5000; 90AP207; 91MI5; 92H225; 94MI10; 96AF800; 98TL841). Similarly, substitution reactions of 3-chlorine atom took place with glycidyl ethers (91MI9) and benzyl alcohols in the presence of potassium *tert*-butoxide. In the case of phenol, the *tert*-butoxy derivative was obtained instead of the phenoxy derivative (96TL4065). Various 5-halo-substituted 1-methyl-6(1*H*)-pyridazinones with different substituents at position 4 were catalytically dehalogenated. If an azido group was at position 4, this was first reduced to an amine, followed by dehalogenation (98JHC819). 1,2-Disubstituted 4- and 5-bromopyridazine-3,6-diones reacted with sodium arylthiolates in dry DMF at room temperature to give *ipso* substitution products (4- or 5-), but they react with sodium benzenethiolate in dry MeOH at room temperature to give both *ipso* and *cine* substitution products (91PJC1085; 92PJC935).

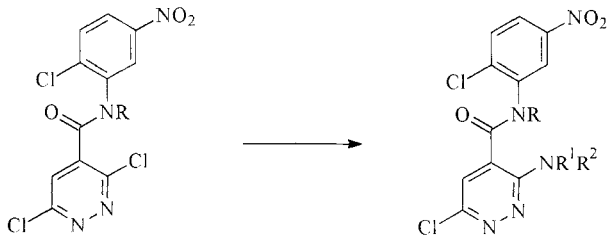
In the series of dihalopyridazines the majority of transformations were carried out with 3,6-dichloropyridazines. Various groups could be attached through halogen exchange to the pyridazine nucleus with formation of a C–C bond. Examples include a reactive methyl group (preparation of pyri-

dazine analog of the natural thyroid hormone thyronine) [88CI(L)109, 88JCS(P1)3085, 88JCS(P1)3097, 88JCS(P1)3103]. The reaction with phenylacetonitrile was used for the syntheses of phenyl 3-pyridazinyl ketone (94SC773) or its 2-fluorophenyl analog [94H(38)125], preparation of 3-indolylpyridazine (90JOC5418), and 3,6-bis-(perfluorooctyl)pyridazine (95JFC113). From 3,6-dichloro-(dibromo or diiodo) pyridazine and activated methylene-phosphonic or -phosphinic acids various **145** were prepared [94H(38)2695] and 3,6-diiodopyridazine yielded 3,6-(diphenylethinyl)pyridazine in a Pd– and Cu–catalyzed reaction (91CJC972). Fluorination of 3,6-dichloropyridazine with fresh HF at 100°C afforded a mix-



(145)

ture of the 3-fluoro-(44%) and 3,6-difluoro (56%) compounds (93CL509). Regioselectivity in substituted 3,6-dichloropyridazines with an alkoxy, amino, or piperidino group were studied and depending on the reaction conditions the nucleophile can displace either the chlorine atom at positions 3 or 6 [92PHA679; 94PHA575; 97H(45)2385]. Of the three chlorine atoms of **146,** the 3-chlorine atom was selectively substituted with alkylamines or cyclopropylamine to give **147** (97AP29, 97JHC1421). The reaction between 3,6-dichloropyridazine and tertiary amines proceeded with dealkylation. When using alkyl dimethylamines, the methyl group usually becomes the leaving group, exceptions are the benzyl or dimethylaminomethyl groups, which are eliminated rather than the methyl group (92SC787). 3,6-Dichloropyridazine was used as starting material when



(146) (147)

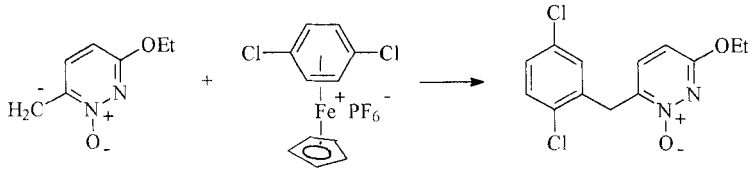
reacting with piperazine or substituted piperazines(92AP187, 92MI8; 93MI6), theophylline (91AP999), aminobenzodioxanes (89AP833), glycidyl ether (94CPB1609), 4-phenoxyphenoxide (95MI2), polyethyleneglycol (96S609), aminophenols (94MI1; 95MI1), hydroxy (or mercapto) alkylamines (95CPB247), and 4-mercaptophenol (92MI1). With 1,2- or 1,3-alkanedithiols or thioalkanedithiols, pyridazine-ring-containing macrocycles of various sizes were prepared (92CJC1886, 92CJC2709; 93CJC1086, 93IC4063).

There have been many investigations concerning the reactivity of the 4,5-dihalo-3(2*H*)-pyridazinones. It has been generally accepted that the halogen at position 5 is preferentially substituted. This has been the case in several recent investigations on *N*-protected derivatives when using alkoxides, phenol, or nitrogen nucleophiles (89M329; 92JHC825; 93BMC2713; 94JHC1199; 95AP654, 95JHC1473, 95MI5; 96JHC1579; 97MI4; 98JHC595, 98JHC601). The kinetics of hydrolysis is in accord with these findings (89MI4). Detailed investigations of solvent effect concerning the product distribution revealed that in nonpolar solvents when using alkoxides only 4-substitution occurred, in moderately polar solvents (acetone, 2-propanol) mixtures of both isomers are formed, and in polar solvents (DMF, DMSO) only the 5-isomer was obtained. The only exception was acetonitrile in which a 3:2 mixture of the 4- and 5-isomers was formed. Similar results were found when using thiols (88JHC1757) or amines and the substituent at position 2 of the pyridazine ring influences the substitution ratio (93H519, 93H785; 96JHC583). With Ph_2PLi at $-78°C$ both chlorine atoms were substituted (97ZOB1651).

Regioselectivity was observed also when 3,4- or 3,5-dichloropyridazines were treated with thiolates and substitution occurred at position 4 in the first case and at position 5 in the second case (88JHC1719; 90PJC741).

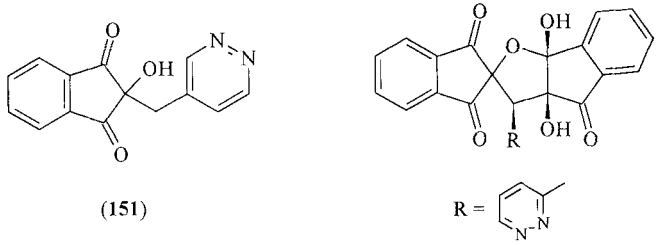
In the group of polyhalopyridazines 3,4,5-trichloropyridazine reacted with alcoholic ammonia at 125°C to give a mixture of the 5-amino (26%) and 4-amino (33%) derivatives (95JHC1423). Tetrafluoropyridazine, when treated with hexafluoroacetone in the presence of CsF at 110°C for 3 days, gave the 4-substituted product in low yield (91OPP760).

Reactions on the alkyl chains or cyano groups attached to the pyridazine nucleus are mainly relegated to methyl groups. 3-Methyl- or 4-methylpyridazines were lithiated and subsequently reacted with alkyl halogenides, aldehydes, ketones, or phenyl isothiocyanate to give addition products in moderate yields [90SL227; 92G503; 94H(39)271]. However, a carbanion of 3-methyl-6(1*H*)-pyridazinone could not be formed satisfactorily with strong bases and instead **148** was used, the carbanion was added to **149,** and the adduct was decomplexed with DDQ to give **150** (89JOMC14). 3-



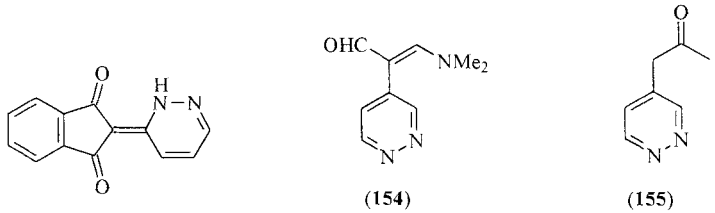
(148) (149) (150)

Propylpyridazine was deprotonated and added to 4-methoxybenzophenone (98MI2). 6-Arylmethyl-3(2*H*)-pyridazinones were reacted with mercuric acetate in acetic acid to give a monomercuri derivative, whereas from 4,5-dihydro-3(2*H*)-pyridazinone a bis-pyridazine mercuri compound was formed(89MI2). 4-Methylpyridazine reacted with ninhydrin to give the adduct **151,** but the 3-methyl analog added initially two molecules of ninhydrin to give finally the spiro compound **152** (96H1665).



(151) (152)

Methyl groups at various positions in the pyridazine ring were condensed with aldehydes to afford styryl derivatives (95JPR347, 95PHA788, 95PJC1642, 95T1585) and 3-methylpyridazine with phthalic anhydride gave **153** [92JCR(S)176]. 4-Methylpyridazine, when submitted to Vilsmeier–Haack formylation afforded **154** and with LDA and 1-acetylimidazole the ketone **155** was obtained (89PHA598).



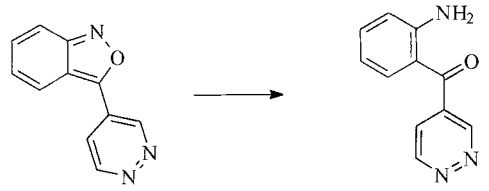
(153) (154) (155)

Some pyridazinecarbonitriles can be hydrolyzed with the use of immobilized biocatalyst and, for example, 6-methylpyridazine-3-carbonitrile gave the acid after 288 h reaction time in good yield (92JHC93). From 3-cyanopyridazine and phenylmagnesium chloride phenyl (3-pyridazinyl) ketone can be prepared (89JHC1787), but from 4-cyano-3(2*H*)-pyridazinone a mixture of the expected phenyl ketone (20%) and 4-phenyl-3(2*H*)-pyridazinone (70%) was obtained (91T8573). By oxidative decyanation of **156** the ketones **157** were prepared (93JHC1685). Phenyl 4-pyridazinyl ketone reacted in a Wittig–type reaction to afford alkenes almost exclusively in the *Z* configuration (91M1055) and its oxime was alkylated with ethyl ω-bromoalkanoates to give a mixture of the *E* and *Z* isomers (96JMC4058). Ketone **159** could be prepared upon catalytic hydrogenation and ring opening of **158** (92AP119). There are also some reports describing reactions on the side-chain of pyridazinium ylids (93MC58; 95ACS778; 97T4411) or on the *N*-(2-oxopropyl) group (91JHC385, 91JHC2079). *O*-Debenzoylation of the nucleosides of the **142** (R=Bz) type was studied and complete deprotection can be achieved with KCN/MeOH (89MI5).

R = Cl, PhCO

(156)

(157)

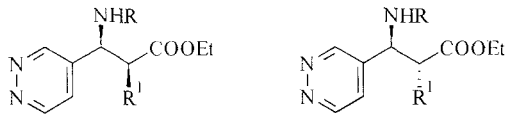


(158)

(159)

For formyl and carboxyl groups, 3,6-diformylpyridazine, prepared by an improved synthesis, was condensed with 1,3-diaminopropane with formation of a 44-membered macrocyclic ring with four pyridazine units [94JCS(CC)487; 96JCS(CC)2579, 96JCS(D)2117]. The 3- and 4-pyridazinecarbaldehydes were reacted with a variety of compounds with a reactive methylene group under the conditions of Knoevenagel–,

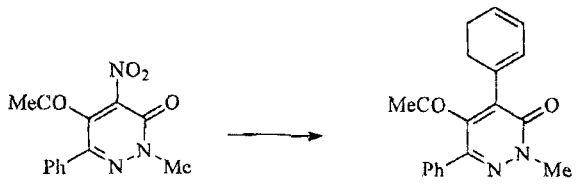
Wittig–Horner–Emmons-, and Hantzsch-type reactions. For compounds where *E, Z* isomerism is possible, the *E* configuration was established for all cases studied (90JHC1313). The same aldehydes and 3- and 4-pyridazinyl alkyl ketones were reacted with thiosemicarbazides, with methyl hydrazinecarbodithioates or with arylsulfonylhydrazides (89AF1196; 92JMC3288; 96MI1). From 4-pyridazinecarbaldehyde and silyloxyketene acetals protected pyridazinylisoserines **160** and **161** were prepared (96H1057). Pyridazinyl aryl or heteroaryl ketones were prepared from 3-pyridazinecarboxylic acid via its chloride or ester (90JHC1645; 91JHC1189; 92JHC1583). 3,6-Dichloro-4-pyridazinecarbonyl chloride was used in a Friedel–Crafts reaction to acylate various aromatic compounds (88HCA988). A podand with two pyridazine rings was prepared from cesium salt of 4-pyridazinecarboxylic acid and α,ω-dichloropolyether (90S773). The anticipated straightforward transformation of an ester into the acid hydrazide was found complicated in case of 3-chloro-6-ethoxycarbonylpyridazine since at elevated temperature the main products were the 3-hydrazino-6-ester, 3-hydrazino-6-acid, and 3-hydrazino-6-acylhydrazide. The 3-chloro-6-acylhydrazide compound was obtained with ethanolic hydrazine at room temperature (94CPB371).



R = *p*-MeOPh, $PhCH_2$
R^1 = OTBDMS

(160) (161)

For nitrogen-containing functional groups, a nitro group at position 3 or 4 in the pyridazine ring is easily displaced and transformed into a halogen atom, an alkylthio, substituted amino, or hydroxy group (94MI8, 94S669; 96JHC1915, 96MI4; 97FA173). Compound **162** reacted in a Diels–Alder reaction with cyclohexa-1,3-diene to give **163**. After cycloaddition the tricyclic adduct undergoes loss of HNO_2 and concomitant ring opening into **163** (93TL161).



(162) (163)

The mesylation of 3-amino-6-chloropyridazine gave exclusively the *N,N*-dimesylated product: no mesylation occurred on the ring-nitrogen atom (89M131). Aminopyridazines were treated with dansyl chloride (97JMC996) or BOC-glycine in the presence of DCC (88AP309) to give the corresponding amides. 3-Pyridazinyl thioureas were transformed with iodomethane under phase-transfer conditions into the corresponding carbodiimides (95JHC13).

3-Hydrazinopyridazines are transformed in a simple and generally applicable method into 3-aminopyridazines after hydrogenolysis with Al/Ni alloy (92JOC3257). The hydrazino group is transformed into a methoxy group with thallium(III) nitrate trihydrate in MeOH (95JOC1466) and *N,N*-dimethylaminomethylene-hydrazinopyridazines are formed with Vilsmeier reagent (94T12933). The chlorine atom in 3-chloro-6-hydrazinopyridazine is practically unreactive toward nucleophiles but it can be activated after the hydrazino group is transformed into a triphenylmethylazo group (89OPP125). 5-Hydrazino-3(2*H*)-pyridazinones usually react with DMAD to give bicyclic products, whereas the *N,N'*-disubstituted analogs gave only the Michael adducts [91JCS(P1)991]. A hydrazino group has been also found to react with pentoses or hexoses or unsubstituted or substituted methyl 1-amino-3-dimethylaminopropenoates (97JHC1115, 97JHC1629).

Aminopyridazines can be obtained in a general transformation in high yields either from azidopyridazines or tetrazolo[1,5-*b*]pyridazines with triphenylphosphine (Staudinger reaction). The intermediate phosphazenes can be hydrolyzed according to three methods (89S666).

For oxygen and other heteroatom-containing functional groups from perhydro 3(2*H*)-pyridazinone after mesylation 3-methanesulfonate was obtained and its stability is unexpectedly high in light of the fact that lactams do not form isolable mesylates (96BMC77). The hydroxy group at position 5 was readily transformed into derivatives of thiophosphoric acid or replaced with an amino, azido group, or chlorine atom (90JHC471). Pyridazine-3-triflates are useful starting material for the formation of 3-alkynylpyridazines [coupling with alkynes in presence of $Pd(PPh_3)_2Cl_2$] or carbomethoxy derivatives (reaction with CO in the presence of Pd complex) [94H(38)1273; 96H1459; review: 94MI5]. Reaction of 3,6-dimethoxypyridazine with hydrazine was reinvestigated and it was shown that it proceeds via 4-amination and not as previously reported at position 5 (93H1313). The 3- and 4-methoxypyridazines react with phenylacetonitrile under basic conditions to give the corresponding acetonitriles **164,** which can be oxidized with oxygen and in the presence of NaH to the corresponding benzoylpyridazines **165** (90H895). 3-Pyridazinylmethyloligonucleotides can be transformed with snake venom phosphodiesterase into mononucleotides (90JA5252). 3-Hydroxy- or mercapto-pyridazines were esterified with *N*-phthalyl amino acids and 4-trib-

(164) (165)

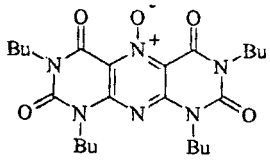
utylstannylpyridazines were useful synthons to give, with bromine or chlorine, the halogenated pyridazines (98T4297).

D. Radical Reactions

There are some new reports concerning radical chlorination (88JOC5704) or bromination at the pyridazine ring although in some cases *N*-methyl bromination product prevails (96MI5). Several reports deal with homolytic alkylation with radicals generated *in situ* from alcohols, carboxylic acids [88JOC5704; 91JHC583; 95H(41)1461], or acylation to yield pyridazinyl ketones or ethoxycarbonylated products (88M751; 89JHC933; 93TL3903; 96H151). A reinvestigation of the reaction of pyridazine with Grignard reagents revealed that the reaction proceeds by homolytic mechanism and a variety of compounds was formed in low yields, such as 3- and 4-alkyl dihydropyridazines and in some cases alkyl and dialkylpyrroles (90ACS279).

E. Oxidations and Reductions

Pyridazine and its 3-methyl analog undergo oxidative biotransformation in rats into monohydroxylated pyridazines, 4,5-dihydroxypyridazine, and its dihydro analogs (89PHA625). *E*-3-(4-Pyridazinyl)acrylate afforded with *m*-CPBA a mixture of 1- (30%) and 2-oxide (40%) and even with excess of *m*-CPBA no epoxide on the side-chain was formed (96H1057). Pyridazine derivatives containing a primary or secondary alcoholic group can be oxidized to the corresponding aldehydes, ketones, or acids with the use of DMSO activated by oxalyl chloride (96JHC2059), SeO_2, or preferentially with MnO_2 (90JHC1377; 95JHC1057; 97CPB1151). Photochemical oxygen-atom transfer from **166** to Emorfazone (an analgesic anti-inflammatory agent) **167a** has revealed that **166** behaves as an efficient agent for both dehydrogenation and oxygenation. In addition to deoxygenated **166** and starting **167a** four compounds were formed: the tetrahydro analog **167b** (14%), compound **168** (2%), and two pyrazolones (28 and 30% yields) by unprece-



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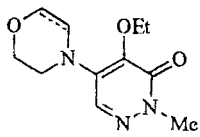
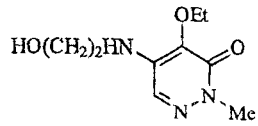


(167a)
(167b)



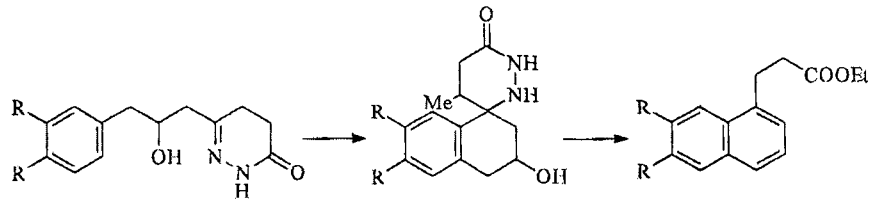
(168)

dented photo-oxidative pyridazine ring contraction (88CPB1714). The same agent when applied to 3-methylpyridazine 2-oxide was found to act via an "oxene" mechanism [90JCS(P1)863, 90JCS(P1)3339]. 4-Arylmethylpyridazines were oxidized to the corresponding ketones with $Na_2Cr_2O_7$ in AcOH [91ZN(B)1720]. Dihydropyridazines were efficiently aromatized under mild conditions with $CuCl_2$ in MeCN via halogenation and spontaneous elimination of HCl (95S1240), with CAN (96PHA528), or by activated MnO_2(93CPB156).

One double bond of 1,4-dihydropyridazines can be selectively reduced with triethylsilane in TFA (96PHA528); tetrahydropyridazines can be reduced to the perhydro analogs by hydroboration (91AKZ259), hydrogenation [93JCS(CC)1179], or electrochemical reduction (90MI2). 3,3,6,6-Tetramethyl-3,4,5,6-tetrahydropyridazine-1-oxide was first deoxygenated and then reduced to the hexahydropyridazine derivative with benzhydryl radicals (89JA1830). 4,5-Dicyanopyridazine was transformed into 4-cyanopyridazine via the 1,4-dihydro derivative and elimination of HCN by reaction with cyclohexa-1,4-diene at 110°C; hydrogen transfer from cyclohexadiene takes place (96JOC6028). Azidopyridazines are efficiently reduced to the amino compounds either with H_2S (96S838) or with triphenylphosphine (89S666).

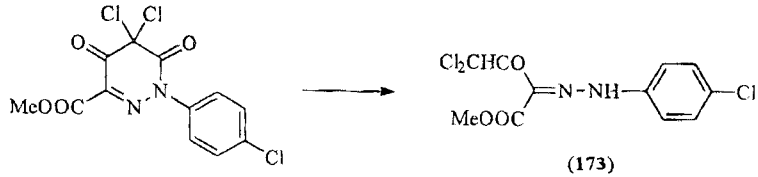
F. Ring Opening and Rearrangements

Thermal decomposition of pyridazine was investigated by IR laser photolysis. Only acetylene and HCN were detected by GC-MS in a ratio of 1:2 [98JCS(P2)269]. *N*-Protected 1,2,3,6-tetrahydropyridazines are readily isomerized into their 1,2,3,4-tetrahydro analogs in the presence of ruthenium complexes (88JOM215). An unusual transformation of **169** with trimethylsilyl triflate (TMST) was observed. The resulting naphthylpropionic acid **171** is formed via a spiro compound **170,** which was isolated in one case (93TL3777; 94MI3). Compound **172,** obtained by chlorination, is unstable and on silica gel column ring opening and decarboxylation led to **173** (90M565). Conversion of 4,5-dicyanopyridazine into substituted 1,2-



(169) (170) (171)

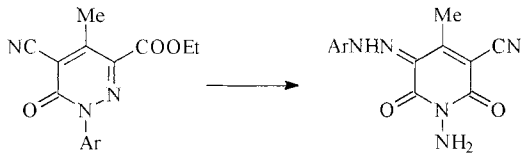
R = OMe



(172) (173)

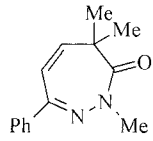
dicyanobenzenes takes place with various alkenes, alkynes, or enamines as [4 +2]-cycloaddition and elimination of nitrogen [95JCS(CC)2201; 97T11711; 98T1809, 98T10851].

Compound **14,** when treated with benzaldehyde, was rearranged into an *N*-aminopyrrolidone derivative [93JCS(P1)1931] and mechanistic interpretation is presented. A previously reported pyridazine–pyrazole contraction was investigated using labeled pyridazine; a carbonium ion is proposed as a reasonable intermediate (89JHC1009). 1-Alkoxycarbonylaminopyrroles were obtained after treatment of 1-alkoxycarbonyl-1,4-dihydropyridazines with TFA (98JOC9880). At a level of dichlorination of 2-phenyl-6-hydroxy-3(2*H*)-pyridazinone rearrangement to *N*-aminopyrrole-2,5-diones takes place (89JHC1649). Pyridazine **174** to pyridine **175** transformation was ob-



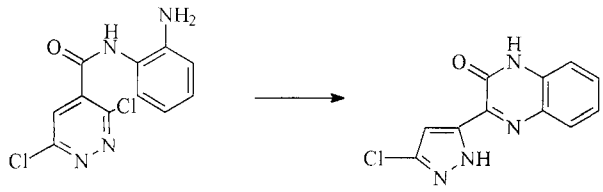
(174) (175)

served with hydrazine (97PS133) and after 1,3-dipolar cycloaddition with 2-diazopropane 2-methyl-6-phenyl-3(2*H*)-pyridazinone yielded, among other products, **176.** Yields vary, depending on the solvent polarity (90T6915).



(176)

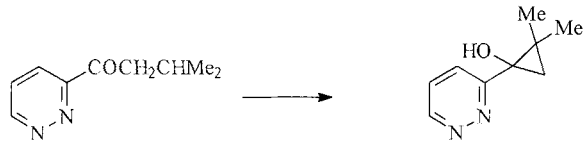
O,N and *O,S* rearrangement of 3- or 4-alkoxypyridazines to a neighboring ring-nitrogen atom or a neighboring thiol group has been recorded [89H(29)67; 96CCC437]. In an attempted cyclization with NaH in DMF **177** was transformed into **178** [94H(38)2081].



(177) (178)

G. Photochemical and Other Transformations

3-Isopropyl-4,5,6-*tert*-butylpyridazine, which exists in the twist conformation, is transformed upon photolysis into the corresponding 1,2–Dewarpyridazine, which is stable (91AG1495). Irradiation of the ketone **179** with UV light produces about 10% of **180** (92JA1838). Photooxidative decomposition of 3,3,6,6-tetraalkyl-substituted perhydropyridazines was investigated and it was found that decomposition is stereospecific and that the 1,4-biradical determined the stereochemical outcome and not the 1,4-cation radical. Cyclobutane and 1-butene derivatives were products identified (93JA4925).



(179) (180)

Bis-cinchona alkaloid complexes with a 3,6-pyridazine bridge and 1,4-dihydroquinidyl- or 1,4-dihydroquinilyl-pyridazines were studied in the osmium-catalyzed enantioselective dihydroxylation of alkenes and were useful for the kinetic resolution of 1-substituted allylic alcohols (93JA3828, 93JA12579; 94TL543, 94TL2861, 94TL6559; 95JA10817; 96TA2805).

Stable 1-(6-aryl-3-pyridazinyl)-3-hydroxypyridinium chlorides gave with triethylamine unstable hydroxypyridinium betaines, which were transformed into unstable dimers. They could not be isolated but their formation was monitored by IR technique (92CCC1951, 92PJC1015).

V. Theoretical Aspects and Physical Properties

A. Calculations

Pyridazine and its derivatives have been extensively studied by a variety of computational methods to correlate the predicted values of their physical properties with the measured ones. As for other azines also for pyridazine several methods were used to calculate its thermodynamic stability, molecular geometry, electron density distribution, ionization potentials, and dipole moments (89KGS1587; 91RRC399) and the significance of different criteria for assessing the π-electron delocalization were also reviewed (92H1631).

Molecular geometry and harmonic force field determined by *ab initio* Hartree–Fock calculations showed a lower aromatic character of pyridazine than expected earlier (93JPC1356). The geometries of some cardiotonic dihydropyridazines were optimized by the MNDO MO method [95JST(332)171] or with the Allinger's MM2(85) program (90JMC1591). The properties of the pyridazine $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ singly excited states were calculated by CASSCF method (92JPC9204) and its fundamental molecular vibration frequencies were determined by MP2 and DFT methods (95MI6; 98MI3). Static dipole polarizabilities and dipole moments of pyridazine and other azines were predicted by *ab initio* electron-correlated calculations and found to be in good agreement with the experimental data (94MI6, 94MP557). The accurate ionization energy and correct ordering of the cationic state of pyridazine were calculated by P3 quasi-particle method (96JCP2762). The quantum yield of the triplet formation of pyridazine in the liquid phase at room temperature was measured by a transient grading method: a relatively small quantum yield and very short triplet lifetime were observed compared to those in the solid phase [92CPL(189)560].

The aromaticity of pyridazine was studied by the spin-coupled theory and it was shown that the Kekulé structure with singlet coupling of π-

electrons on the adjacent nitrogen atoms contributes 20.5%; the other Kekulé form has an occupation number of 54% and both Dewar structures contribute only 8.5% each [89JCS(P2)255]. Similarly the aromaticity of pyridazine was estimated by principal component analysis (PCA) (89JA7). A unified aromaticity scale was introduced for several azines and for pyridazine the aromaticity index (I_A) was estimated as $I_A = 79$ (for pyrimidine $I_A = 84$ and for pyrazine $I_A = 83$) (92T335). The aromaticity indices were also calculated for 4,5-dichloro-3(2*H*)-pyridazinone, 3(2*H*)-pyridazinethione (92T857), and for one pyridazinium betaine [94H(37)249]. The measured ^{1}H-NMR long-range coupling constants $^4J_{Me,H5}$ and $^4J_{Me,H3}$ for 4-methylpyridazine were also used to estimate the extent of π-electron delocalization in the pyridazine ring (92JHC935). In addition, the aromaticity descriptors were used in the experimental design of pharmacologically interesting pyridazines (93QSAR146).

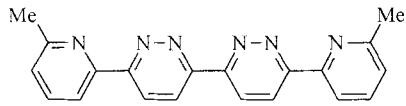
The C–H and N–H deprotonation of pyridazine (92MI5, 92ZOB2319) and its methyl derivatives were calculated by INDO and AM1 methods (92ZOB2100). The AM1 method was also used to calculate the aromatization energy and heats of formation of pyridazine [89H(28)1135].

Density functional calculations were used to determine protonation enthalpies, geometric parameters, and dipole moments of pyridazine (94T2405) as well as the total energy values for 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone [94H(38)1957]. The same physical properties were calculated also by MM3 force-field methods (93JA11906) and by statistical methods based on spectroscopic data (94JIC195).

Theoretical methods were used to predict the course of some transformations and nature of reaction intermediates involving pyridazines, i.e., the intermediate of bis(dihydroxyquininidine)-3,6-pyridazine osmium-catalyzed dihydroxylation of styrene was characterized theoretically by IMOMM calculations (97JOC7892). In a similar fashion the regiochemistry of the [3 + 2] cycloaddition of pyridazinium ylids to acrylates and propiolates (96T8853) and the formation of pyridazines in Diels–Alder reactions of 1,2,4,5-tetrazines with acetylenes (93JA1353) were studied. The gas-phase pyrolysis of 3-ethoxypyridazine (92MI6) and thermal decomposition of pyridazine were also studied theoretically [95JCS(F1)1587].

Pyridazine was evaluated for hydrogen bond acceptor properties of its ring nitrogens on the basis of computed molecular electrostatic properties [94JCS(P2)199] and as a proton acceptor against 4-nitrophenol [89JCS(P2)1355]. The solute proton donor and acceptor scales were designed on the basis of the hydrogen bond acceptor behavior of pyridazine and other heterocycles for the use in drug design (94JPO743). Pyridazine complexing ability was measured [95JST(354)141] and charge-transfer complexes with iodine were investigated spectrometrically (96MI2). Stable

monolayers at the air–water interface were formed between cyclic dimers of long-chain derivatives of Kemp's acid, which served as a molecular cleft for the specific binding of pyridazine (91JA7342). Pyridazines with a substituted phenyl or biphenyl group at position 6 and a hexyl side-chain at position 3 show mesophase behavior (94NJC643). Compound **181,** prepared from 3-chloro-6-methoxypyridazine and 2-methyl-6-trimethylstannylpyridine in the presence of $Pd(PPh_3)_4$, is self-organized in the presence of $AgCF_3SO_3$ into a supramolecular network consisting of parallel vertical and horizontal chains complexed with the silver ligand (94AG2432).



(181)

B. Basicity and Tautomerism

Tautomerism of substituted pyridazinones and pyridazinethiones has been extensively studied by theoretical and experimental methods. In the case of "maleic hydrazide" the computational methods predicted the monohydroxy monoketo tautomer to be predominant in the gaseous phase as well as in aqueous solution where the solvation was predicted to stabilize the diketo form [93JCS(P2)331]. Infrared spectroscopy-based studies in low-temperature inert gas matrices of 3(2*H*)-pyridazinone and its thio analog showed that the stability of the thiol form with respect to the thione form was considerably higher than that of the hydroxy form with respect to the oxo form (92JPC6250). Although in the case of 3(2*H*)-pyridazinethione in inert gas matrices the thione form was present exclusively, the compound underwent UV-induced photoisomerization in matrices, giving predominantly the thiol tautomer (91JPC2404). Similarly, on basis of their IR spectra, 3(2*H*)-pyridazinone and its 4,5-dichloro derivative were found to exist only in lactam forms in the solid phase, but in dioxane an equilibrium with the lactim form exists (97MI8). For 6-(*p*-bromophenyl)-3(2*H*)-pyridazinone the lactim form was found to be predominant in strongly alkaline solutions, whereas at neutral pH the equilibration with the lactam form exists (94RRC991). The equilibria between 6-arylpyridazine-3(2*H*)-thiones and their tautomeric iminothiol forms were also investigated by IR (92PS299). For the first time, in an argon matrix at low temperature, 3-hydroxypyridazine was isolated and at higher temperatures it was transformed into 3(2*H*)-pyridazinone [90SA(A)1087]. From their IR and UV spectra as well

as the pK_a values of 2,4- and 2,5-disubstituted 3(2*H*)-pyridazinones it was established that the latter form strong intramolecular hydrogen bonds, S-H···O, but the 5-thiols exist only as such (88MI2). The tautomerism of four isomeric hydroxypyridazine *N*-oxides was studied theoretically by high-level *ab initio* methods. Hydroxy *N*-oxide tautomers were predicted to be substantially favored in case of 3-hydroxy- and 5-hydroxy-pyridazine 1-oxides both in solution and in gas phase, but 6-hydroxypyridazine 1-oxide was predicted to be favored as *N*-hydroxy-oxo tautomer in both phases; however, no firm conclusion has been reached for 4-hydroxypyridazine 1-oxide (97MI7).

The observed basicity of pyridazine was interpreted by several computational methods; with *ab initio* SCF-MO calculations it was found that the magnitude of ε_{homo} parallels the observed basicity [95JST(339)255] and the pK_a value of pyridazine in water solution was correlated with the total atomic charge and the ionization potential, calculated by the MOSP method (92RRC819). Protonation constants were determined by potentiometry and UV spectrophotometry for some pharmacologically interesting substituted 3-amino-6-phenylpyridazines. Their basicity was strongly dependent on the nature of both the substitutents on the pyridazine ring and on the side-chain [90JCS(P2)1191; 94JCR(S)4].

C. Spectra

Both ^{1}H- and ^{13}C-NMR spectroscopy has been used to study the structural properties of several pyridazines. The molecular structure of pyridazine was investigated by direct couplings obtained from the NMR spectra recorded in an oriented nematic liquid–crystal solvent. These measurements combined with microwave and electron diffraction data gave the mean C–C bond length in pyridazine (139.5 pm), which was found to be closely comparable to that in benzene, and the N–N and C–N bond lengths of pyridazine were found to be very similar in the gas phase (90MI5). Deuterium isotope effects on the ^{13}C-NMR shifts on the ring-carbon atoms of pyridazine were investigated and it was found that one-bond isotope shifts reflect the MNDO MO calculated C–H bond lengths, two-bond shifts depend on the nature of the observed sites, and three-bond shifts are controlled by the hetero atoms existing in the coupling pathway (92BCJ2894). The ^{13}C-NMR spectrum of pyridazine was simulated by a parametric computational technique and the high predictive ability of this method was found also for other azines (95AJC1267). *Ab initio* calculations based on nuclear shielding tensors in ^{13}C- and ^{15}N-NMR spectra of pyridazine and other azines and the correlation effects were found to consis-

tently increase the isotropic shieldings [92CPL(197)59]. The ^{17}O-NMR chemical shifts were also measured for pyridazine *N*-oxide and compared with the values of other diazine *N*-oxides (89T3613).

The ^{13}C-NMR spectra were recorded and unambigously assigned for *N*-methylpyridazinium iodide (96MRC728) and a large set of 3,6-disubstituted and 2,4,5-trisubstituted pyridazines (90MRC380; 91CJC972). The aza effect was measured in ^{13}C-NMR spectra of 3- and 4-acetylpyridazine (93KGS202) and protonation of some dihydropyridazines in concentrated sulfuric acid was also studied by ^{13}C-NMR (90KGS960). The ^{13}C-NMR and NOE measurements were used to determine the stereochemistry of several biologically active pyridazines and oximes of aryl 3- and 4-pyridazinyl ketones [89H(29)1399; 91CCC2251; 93MI1; 96H151; 97JMC4420]. Electron donor–acceptor interactions between pyridazine and various aromatic hydrocarbons were also studied by NMR. Pyridazine was found to be a weak electron acceptor in the complexes studied (89AJC1313).

Fragmentation patterns in electron impact mass spectra were studied of various 4,5-dihydro-3(2*H*)-pyridazinones (91OMS1082), of some pyridazinyl phosphinothioates [94PS(91)9], and of 3- and 4-substituted pyridazines, where a clear differentiation between isomers on the basis of their fragmentation was possible (91OMS595, 91RCM421). In general it was found that 3- and 4-substituted pyridazines gave highly stable molecular ions in their EI mass spectra (91MI2).

High-pressure mass spectrometry was used to measure the equilibration constants for the electron transfer between di- and polyalkylpyridazines and their cation radicals (88JA7945). Mass-resolved excitation spectrum was also used to determine the lifetime of the Rydberg state of pyridazine (95JCP4907).

Infrared and Raman spectra of pyridazine in the vapor and condensed phases were recorded using both parallel and perpendicular polarization of light (98MI3). With the aim to correctly assign the vibrational spectra of pyridazine the vibrational frequencies and geometry were calculated by the B3LYP method (96JPC6973). The chloro substitutents in 3,6-dichloropyridazine were found to shift the vibrational frequencies of the pyridazine ring to higher frequencies when compared to those for pyridazine itself (94MI7). Infrared spectra of 3-methyl- and 3,4,5-trichloropyridazine were also studied (91MI6). Vibrational frequencies of 3,6-dichloropyridazine were studied by laser spectrum at 200–4000 cm^{-1} and assigned assuming the C_{2v} point group symmetry (93MI3).

Several new, low-lying electronic states of pyridazine were identified by comparison of its V/UV spectra and near-threshold electron-energy-loss spectra (91MI7) and (π, n) states of pyridazine were studied theoretically by *ab initio* CIS calculations of its electronic spectrum (95CP183).

Gas–electron diffraction spectroscopy was used to determine the gas-phase molecular structure of 3,6-dichloropyridazine [97JCS(P2)857]. The depolarized Rayleigh spectrum of pyridazine was recorded from 267 to 347 K. The observed nonlinearity between the Stokes–Einstein–Debye plot of reorientation time vs viscosity/temperature was attributed to increasing dipole–dipole interactions at lower temperatures (90MI1). Resonance multiphoton ionization spectroscopy (REMPI) was used to locate the lowest Rydberg state B_2n-3*s* of pyridazine (92JSP215) and pyridazine was also investigated by the degenerated four-wave mixing (DFWM) technique and its DFWM spectrum was found to be in good agreement with the previously reported absorption spectra (97CPL272).The adsorption of pyridazine and pyridazine-4-carboxylic acid from aqueous solutions at well-defined Pt(111) electrode surfaces was studied by Auger spectroscopy and surface vibrational spectra of the adsorbed layers were obtained by energy–loss spectroscopy (EELS) (90L1273). The influence of the ring substituents on the electron absorption spectra of some pyridazinium ylides was studied (93RRC759) and further studies by electron absorption spectroscopy and electron diffusion spectroscopy showed that pyridazinium ylids, depending on the nature of the solvent, are able to take part in dipolar orientation induction interactions as well as in proton donor–acceptor interactions [93MI7; 94JCP419].

D. X-Ray Structure Determinations

The crystal structures of many pyridazines were determined to support structure/activity relationship predictions of some biologically active compounds and also to determine some structural parameters of the compounds studied. The structures of anticonvulsant drugs 1-[6-(2-chlorophenyl)-3-pyridazinyl]piperidin-4-ol [89AX(C)102] and 1-[6-(4-chloro-2-methylphenyl)pyridazin-3-yl]piperidin-4-ol [89JCS(P2)449] as well as the 6-phenyl-substituted 3(2*H*)-pyridazinone–derived cardiovascular agents [94AX(B)71], vasodilator Prizidilol [94AX(B)68], and an antiviral drug, 4-{2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethoxy} benzoate [91AX(C)1517], were determined. Employing X-ray structural analysis the binding of the 3,6-disubstituted pyridazine possessing the tetrazole substituent to human rhinovirus (HRV14) was also studied [95AX(D)496].

The X-ray structure of pyridazine itself at 100 K showed that the determined valence angles agreed closely to those obtained by combined analysis of electron diffraction, microwave, and liquid–crystal NMR data. Significant differences were, however, observed in bond lengths, which were attributed to the crystal packing effect [91AX(C)1933]. An X-ray

analysis of 3-isopropyl-4,5,6-*tert*-butylpyridazine revealed that the pyridazine ring exists in a twist conformation (91AG1495). The X-ray structures were also determined for 3-chloro-6-methoxy-5-tosylmethylpyridazine [92AX(C)1504]; 3-chloro-5-tosylmethylpyridazine (94PJC255); 4-chloro-3,6-bis(chloromethyl) pyridazine, where the shortening of the pyridazine C4–C5 bond was observed [89AX(C)1327]; 5-(2-chlorobenzyl)-6-methyl-3(2*H*)pyridazinone [95AX(C)1834]; and 4-(hydroxyimino)-2-methyl-1-(2-phenylethyl)hexahydropyridazine (93IZV539). The previously attributed structure to 5-arylidene-4,5-dihydropyridazines **12** has been reinvestigated and on the basis of ^{1}H-NMR NOE measurements and X-ray analysis these compounds should be represented as aromatic pyridazine tautomers **13** (95AJC1601).

Employing X-ray analysis, the structures of some of the reaction products of ethyl (*Z*)-5-aryl-2-diazo-5-hydroxy-3-oxopent-4-enoates with triphenylphosphine were determined as 6-aryl-3-ethoxycarbonyl-4-hydroxypyridazines (97MI2). The reaction product of two molecules of 6-(2-thienyl)-2,3,4,5-tetrahydro-3-pyridazinone with one molecule of hydrazine hydrate was also characterized and the N–N bond between two pyridazine rings in a dimeric structure of the product was found to be partially double (88MI1). X-ray analysis also revealed the nonplanarity of the pyridazine ring in [7](3,6)pyridazinophane **59** (89TL4649). In an unusual transformation of triazolopyridazine **69** with potassium *tert*-butoxide the hexahydropyridazine **70** was obtained with 91% ee and its absolute stereochemistry was determined on the basis of the X-ray structure of its precursor **69** (94S66). The structure of the mesoionic pyridazinium sulfonate **72,** unexpectedly formed by ring transformation of 1λ^6,2-thiazine **71,** was also obtained by X-ray analysis [94AX(C)1150]. Pyridazinylphosphonic acids **145** were analyzed and in crystalline form they exist in the *Z* configuration [94H(38)2695]. Products of pyridazine transformations **178** [94H(38)2081] and **152** (96H1665) were determined by X-ray analysis.

Polymorphism was studied in the cases of 3-amino-1-(*m*-trifluoromethylphenyl)-6-methyl-4(1*H*)-pyridazinone (92JPS836) and of "maleic hydrazide," where its new polymorph was investigated [93AX(C)36]. Hydrogen bonding in crystal structures was studied with four substituted 3(2*H*)-pyridazinones: extensive hydrogen bonding was found in crystalline structures of 5-methyl- and 6-methyl-3(2*H*)-pyridazinones; 4-methyl-3(2*H*)-pyridazinone forms hydrogen-bound dimers [96AX(C)2622]. Conformational studies in the solid state were performed with some partially unsaturated pyridazine-1,2-dicarboxylates, where it was found that diethyl 3,6-diphenyl-1,2-dihydropyridazine-1,2-dicarboxylate adopts a twist-boat conformation, whereas diethyl 3,6-diphenyl-1,2,3,6-tetrahydro-pyridazine-1,2-dicarboxylate adopts in the solid state the half-chair conformation—the same as in solution [89JCS(P2)1887].

REFERENCES

88ACH631 N. G. Kandile, E. A. El-Oawi, V. R. Seliem, and M. F. Ismail, *Acta Chim. Hung.* **125,** 631 (1988).

88AP309 N. Haider and G. Heinisch, *Arch. Pharm. (Weinheim, Ger.)* **321,** 309 (1988).

88AP509 N. M. Fathy, F. M. A. Motti, and G. E. H. Elgemeie, *Arch. Pharm. (Weinheim, Ger.)* **321,** 509 (1988).

88CB2007 W. Sucrow, K.-H. Ellermann, U. Flörke, and H.-J. Haupt, *Chem. Ber.* **121,** 2007 (1988).

88CCC1297 T. Gracza, Z. Arnold, and J. Kovač, *Collect. Czech. Chem. Commun.* **53,** 1297 (1988).

88CI(L)30 F. M. Abdelrazek, A. W. Erian, and A. M. El Torgoman, *Chem. Ind. (London)*, 30 (1988).

88CI(L)109 N. Lewis, *Chem. Ind. (London)*, 109 (1988).

88CPB1558 C. Rubat, P. Coudert, J. Couquelet, P. Bastide, and J. Bastide, *Chem. Pharm. Bull.* **36,** 1558 (1988).

88CPB1714 Y. Maki, K. Shimada, M. Sako, Y. Kitade, and K. Hirota, *Chem. Pharm. Bull.* **36,** 1714 (1988).

88CPB5000 C. Rubat, P. Coudert, P. Bastide, and P. Tronche, *Chem. Pharm. Bull.* **36,** 5000 (1988).

88FA539 G. A. Pinna, M. M. Curzu, D. Barlocco, G. Cignarella, E. Cavalletti, M. Germini, and K. Berger, *Farmaco* **43,** 539 (1988).

88G187 M. T. Cocco, C. Congiu, A. Maccioni, and A. Plumitallo, *Gazz. Chim. Ital.* **118,** 187 (1988).

88HCA988 T. A. Eichhorn, S. Piesch, and W. Ried, *Helv. Chim. Acta* **71,** 988 (1988).

88JA7945 S. F. Nelsen, D. T. Rumack, and M. Meot-Ner (Mautner), *J. Am.Chem. Soc.* **110,** 7945 (1988).

88JCS(P1)3085 P. D. Leeson and J. C. Emmett, *J. Chem. Soc., Perkin Trans. 1*, 3085 (1988).

88JCS(P1)3097 D. M. B. Hickey, P. D. Leeson, S. D. Carter, M. D. Goodyear, S. J. Jones, N. J. Lewis, I. T. Morgan, M. V. Mullane, and J. Y. Tricker, *J. Chem. Soc., Perkin Trans. 1*, 3097 (1988).

88JCS(P1)3103 D. M. B. Hickey, P. D. Leeson, R. Novelli, V. P. Shah, B. E. Burpitt, L. P. Crawford, B. J. Davies, M. B. Mitchell, K. D. Pancholi, D. Tuddenham, N. J. Lewis, and C. O'Farrell, *J. Chem. Soc., Perkin Trans. 1*, 3103 (1988).

88JHC1535 P. Mátyus, G. Szilágyi, E. Kasztreiner, G. Rabloczky, and P. Sohár, *J. Heterocycl. Chem.* **25,** 1535 (1988).

88JHC1543 C. B. Ziegler, N. A. Kuck, S. M. Harris, and Y. Lin, *J. Heterocycl. Chem.* **25,** 1543 (1988).

88JHC1689 B. E. Burpitt, L. P. Crawford, B. J. Davies, J. Mistry, M. B. Mitchell, K. D. Pancholi, and W. J. Coates, *J. Heterocycl. Chem.* **25,** 1689 (1988).

88JHC1719 P. H. Olesen, T. Kappe, and J. Becher, *J. Heterocycl. Chem.* **25,** 1719 (1988).

88JHC1757 J. W. Lyga, *J. Heterocycl. Chem.* **25,** 1757 (1988).

88JOC5704 R. E. Hackler, B. A. Dreikorn, G. W. Johnson, and D. L. Varie, *J. Org. Chem.* **53,** 5704 (1988).

88JOM215 G. Menchi, U. Matteoli, A. Scrivanti, S. Paganelli, and C. Botteghi, *J. Organomet. Chem.* **354,** 215 (1988).

88LA1005 M. H. Elnagdi, N. S. Ibrahim, K. U. Sadek, and M. H. Mohamed, *Liebigs Ann. Chem.*, 1005 (1988).

88M751 W. Dostal, G. Heinisch, and G. Lötsch, *Monatsh. Chem.* **119,** 751 (1988).

88M985 K. Gewald, M. Gruner, U. Hain, and G. Süptitz, *Monatsh. Chem.* **119,** 985 (1988).

88MI1 I. S. A. Farag, M. A. El Kordy, and G. Will, *Cryst. Res. Technol.* **23,** 723 (1988).

88MI2 Š. Kovač, V. Konečný, and V. Knoppová, *Chem. Pap.* **42,** 73 (1988) [*CA* **110,** 38489 (1989)].

88S89 L. W. Singh, H. Ila, and H. Junjappa, *Synthesis,* 89 (1988).

88SC2183 N. Kalyanam, K. G. Dave, and M. A. Likhate, *Synth. Commun.* **18,** 2183 (1988).

88SC2225 C. E. Adams, D. Aguilar, S. Hertel, W. H. Knight, and J. Paterson, *Synth. Commun.* **18,** 2225 (1988).

88TL3927 U. Pindur and M.-H. Kim, *Tetrahedron Lett.* **29,** 3927 (1988).

89AF1196 J. Easmon, G. Heinisch, W. Holzer, and B. Rosenwirth, *Arzneim.-Forsch.* **39,** 1196 (1989).

89AG1288 K. P. Hartmann and M. Heuschmann, *Angew. Chem.* **101,** 1288 (1989).

89AJC1313 D. T. Hurst, H. B. Thakrar, C. H. J. Wells, and J. Wyer, *Aust. J. Chem.* **42,** 1313 (1989).

89AP535 G. H. Elgemeie, H. A. Elfahham, Y. R. Ibrahiem, and H. H. Elnagdi, *Arch. Pharm. (Weinheim, Ger.)* **322,** 535 (1989).

89AP833 S. Corsano, G. Strappaghetti, and A. Codagnone, *Arch. Pharm. (Weinheim, Ger.)* **322,** 833 (1989).

89AX(C)102 J. N. Lisgarten and R. A. Palmer, *Acta Crystallogr., Sect. C* **C45,** 102 (1989).

89AX(C)1327 P. F. Abraham, B. Mernari, M. Lagrenée, and S. Sueur, *Acta Crystallogr., Sect. C* **C45,** 1327 (1989).

89BCJ2608 J. Nakayama, T. Konishi, A. Ishii, and M. Hoshino, *Bull. Chem. Soc. Jpn.* **62,** 2608 (1989).

89CPB2832 C. Rubat, P. Coudert, P. Tronche, J. Bastide, P. Bastide, and A.-M. Privat, *Chem. Pharm. Bull.* **37,** 2832 (1989).

89G95 S. A. S. Ghozlan, M. H. Mohamed, A. Y. Soliman, and H. Bakeer, *Gazz. Chim. Ital.* **119,** 95 (1989).

89H(28)1085 P. Desos, G. Schlewer, and C. G. Wermuth, *Heterocycles* **28,** 1085 (1989).

89H(28)1135 M. J. S. Dewar and A. J. Holder, *Heterocycles* **28,** 1135 (1989).

89H(29)67 P. Mátyus, N. Makk, E. Kasztreiner, and G. Jerkovich, *Heterocycles* **29,** 67 (1989).

89H(29)1077 W. J. Coates and A. McKillop, *Heterocycles* **29,** 1077 (1989).

89H(29)1241 J. Nakayama and A. Hirashima, *Heterocycles* **29,** 1241 (1989).

89H(29)1309 N. Haider, G. Heinisch, and I. Volf, *Heterocycles* **29,** 1309 (1989).

89H(29)1399 J. Easmon, G. Heinisch, and W. Holzer, *Heterocycles* **29,** 1399 (1989).

89H(29)1595 V. Dal Piaz, G. Ciciani, M. P. Giovannoni, and G. Turco, *Heterocycles* **29,** 1595 (1989).

89H(29)1907 A. M. El Massry and A. Amer, *Heterocycles* **29,** 1907 (1989).
89HCA65 U. Pindur, L. Pfeuffer, and M.-H. Kim, *Helv. Chim. Acta* **72,** 65 (1989).
89IJC(B)882 C. V. R. Sastri, K. S. Rao, V. S. H. Krishnan, K. Rastogi, M. L. Jain, R. K. Verma, R. M. Tripathi, P. P. Singh, C. S. Rao, and R. Kaushal, *Indian J. Chem., Sect. B* **28B,** 882 (1989).
89JA7 A. R. Katritzky, P. Barczynski, G. Musumarra, D. Pisano, and M. Szafran, *J. Am. Chem. Soc.* **111,** 7 (1989).
89JA1830 P. S. Engel and W. X. Wu, *J. Am. Chem. Soc.* **111,** 1830 (1989).
89JCS(P2)255 D. L. Cooper, S. C. Wright, J. Gerratt, and M. Raimondi, *J. Chem. Soc., Perkin Trans. 2,* 255 (1989).
89JCS(P2)449 G. Georges, D. P. Vercauteren, G. Evrard, and F. Durant, *J. Chem. Soc., Perkin Trans. 2,* 449 (1989).
89JCS(P2)1355 M. H. Abraham, P. P. Duce, D. V. Prior, D. G. Barratt, J. J. Morris, and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2,* 1355 (1989).
89JCS(P2)1887 M. Kaftory, T. H. Fisher, and S. M. Dershem, *J. Chem. Soc., Perkin Trans. 2,* 1887 (1989).
89JHC169 B. D. Schober, G. Megyeri, and T. Kappe, *J. Heterocycl. Chem.* **26,** 169 (1989).
89JHC933 P. Y. Boamah, N. Haider, and G. Heinisch, *J. Heterocycl. Chem.* **26,** 933 (1989).
89JHC1009 G. Heinisch, T. Huber, C. Langer, W. Gössler, and G. Kollenz, *J. Heterocycl. Chem.* **26,** 1009 (1989).
89JHC1353 M. D. Taylor, K. R. Anderson, and E. W. Badger, *J. Heterocycl. Chem.* **26,** 1353 (1989).
89JHC1649 C. Yaroslavsky, P. Bracha, and R. Glaser, *J. Heterocycl. Chem.* **26,** 1649 (1989).
89JHC1787 G. Heinisch and T. Huber, *J. Heterocycl. Chem.* **26,** 1787 (1989).
89JMC342 I. Sircar, R. P. Steffen, G. Bobowski, S. E. Burke, R. S. Newton, R. E. Weishaar, J. A. Bristol, and D. B. Evans, *J. Med. Chem.* **32,** 342 (1989).
89JMC528 C. G. Wermuth, G. Schlewer, J. J. Bourguignon, G. Maghioros, M. J. Bouchet, C. Moire, J. P. Kan, P. Worms, and K. Biziere, *J. Med. Chem.* **32,** 528 (1989).
89JOC3260 I. Hughes and J. Clardy, *J. Org. Chem.* **54,** 3260 (1989).
89JOC4970 J. E. Oliver, R. M. Waters, and W. R. Lusby, *J. Org. Chem.* **54,** 4970 (1989).
89JOMC14 R. C. Cambie, S. J. Janssen, P. S. Rutledge, and P. D. Woodgate, *J. Organomet. Chem.* **359,** C14 (1989).
89JPR375 N. S. Ibrahim, M. H. Mohamed, Y. Mahfouz, and M. H. Elnagdi, *J. Prakt. Chem.* **331,** 375 (1989).
89KGS1587 B. Ya. Simkin and M. N. Gluhovcev, *Khim. Geterotsikl. Soedin.,* 1587 (1989).
89M131 G. Szilágyi and P. Dvortsák, *Monatsh. Chem.* **120,** 131 (1989).
89M329 U. G. Wagner, C. Kratky, and T. Kappe, *Monatsh. Chem.* **120,** 329 (1989).
89MI1 P. Coudert, C. Rubat, P. Tronche, P. Bastide, and J. Bastide, *Pharm. Acta Helv.* **64,** 159 (1989).
89MI2 N. G. Kandile, A. A. Soliman, and E. A. El Sawi, *Synth. React. Inorg. Met.-Org. Chem.* **19,** 779 (1989) [*CA* **112,** 235463 (1990)].

89MI3 N. G. Kandile, F. S. Sayed, and M. F. Ismail, *J. Chem. Soc. Pak.* **11,** 46 (1989).

89MI4 V. Konečný, J. Muchová, A. Jurášek, and P. Zahradník, *Chem. Pap.* **43,** 547 (1989).

89MI5 S.-G. Lee, S.-Y. Choi, and Y.-J. Yoon, *Bull. Korean Chem. Soc.* **10,** 317 (1989).

89MI6 S.-G. Lee and Y.-J. Yoon, *Bull. Korean Chem. Soc.* **10,** 614 (1989).

89MI7 P. Coudert, C. Rubat, J. Couquelet, J. Fialip, P. Bastide, and A. M. Privat, *Eur. J. Med. Chem.* **24,** 551 (1989).

89OPP125 C. Farina, R. Monguzzi, and M. Pinza, *Org. Prep. Proced. Int.* **21,** 125 (1989).

89PHA598 N. Haider, G. Heinisch, and S. Offenberger, *Pharmazie* **44,** 598 (1989).

89PHA625 H-H. Borchert, S. Pfeifer, B. Helbig, P. Franke, and G. Heinisch, *Pharmazie* **44,** 625 (1989).

89S213 V. Dal Piaz, G. Ciciani, and G. Turco, *Synthesis,* 213 (1989).

89S666 T. Kappe, A. Pfaffenberger, and W. Stadlbauer, *Synthesis,* 666 (1989).

89T3597 M. H. Elnagdi, F. M. Abdelrazek, N. S. Ibrahim, and A. W. Erian, *Tetrahedron* **45,** 3597 (1989).

89T3613 D. W. Boykin and A. C. Baumstark, *Tetrahedron* **45,** 3613 (1989).

89TL4649 P. G. Gassman and G. S. Boardman, *Tetrahedron Lett.* **30,** 4649 (1989).

90ACH829 N. G. Kandile and E. A. Ahmed, *Acta Chim. Hung.* **127,** 829 (1990).

90ACS279 T. Holm, *Acta Chem. Scand.* **44,** 279 (1990).

90AHC385 M. Tišler and B. Stanovnik, *Adv. Heterocycl. Chem.* **49,** 385 (1990).

90AP207 P. Y. Boamah, N. Haider, and G. Heinisch, *Arch. Pharm. (Weinheim, Ger.)* **323,** 207 (1990).

90BCJ652 K. U. Sadek, M. A. Selim, and R. M. Abdel-Motaleb, *Bull. Chem. Soc. Jpn.* **63,** 652 (1990).

90CCC734 M. H. Elnagdi, K. U. Sadek, N. M. Taha, and Y. M. Yassin, *Collect. Czech. Chem. Commun.* **55,** 734 (1990).

90CCC2707 A. Krutošiková, M. Dandárova, and V. Konečný, *Collect. Czech. Chem. Commun.* **55,** 2707 (1990).

90CCC2977 S. El-Kousy, I. El-Sakka, A. M. El-Torgoman, H. Roshdy, and M. H. Elnagdi, *Collect. Czech. Chem. Commun.* **55,** 2977 (1990).

90CPB3009 C. Rubat, P. Coudert, B. Refouvelet, P. Tronche, P. Bastide, and J. Bastide, *Chem. Pharm. Bull.* **38,** 3009 (1990).

90H895 H. Yamanaka and S. Ohba, *Heterocycles* **31,** 895 (1990).

90H1967 E. Raviña, C. Teran, L. Santana, N. Garcia, and I. Estevez, *Heterocycles* **31,** 1967 (1990).

90H2163 B. Singh and G. Y. Lesher, *Heterocycles* **31,** 2163 (1990).

90JA5252 H. Sugiyama, H. Kawabata, T. Fujiwara, Y. Dannoue, and I. Saito, *J. Am. Chem. Soc.* **112,** 5252 (1990).

90JA5654 J. Nakayama and R. Hasemi, *J. Am Chem. Soc.* **112,** 5654 (1990).

90JAN477 M. Nakagawa, Y. Hayakawa, K. Furihata, and H. Seto, *J. Antibiot.* **43,** 477 (1990).

90JCS(P1)863 M. Sako, S. Ohara, K. Shimada, K. Hirota, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1,* 863 (1990).

90JCS(P1)3339 M. Sako, S. Ohara, K. Hirota, and Y. Maki, *J. Chem. Soc., Perkin Trans 1,* 3339 (1990).

90JCS(P2)1191 F. Arnaud-Neu, M.-J. Schwing-Weill, B. Spiess, and R. Yahya, *J. Chem. Soc., Perkin Trans. 2,* 1191 (1990).

90JCS(P2)1943 M. Cabré, J. Farràs, J. F. Sanz, and J. Vilarrasa, *J. Chem. Soc., Perkin Trans. 2,* 1943 (1990).

90JHC205 M. M. Curzu, G. A. Pinna, D. Barlocco, and G. Cignarella, *J. Heterocycl. Chem.* **27,** 205 (1990).

90JHC471 B. D. Schober, G. Megyeri, and T. Kappe, *J. Heterocycl. Chem.* **27,** 471 (1990).

90JHC557 P. G. Baraldi, A. Chiarini, A. Leoni, S. Manfredini, D. Simoni, and V. Zanirato, *J. Heterocycl. Chem.* **27,** 557 (1990).

90JHC579 J.-P. Vors, *J. Heterocycl. Chem.* **27,** 579 (1990).

90JHC707 Y. Tomita, S. Kabashima, T. Okawara, T. Yamasaki, and M. Furukawa, *J. Heterocycl. Chem.* **27,** 707 (1990).

90JHC927 B. Chantagrel, C. Deshayes, B. Pujol, and Z. J. Wei, *J. Heterocycl. Chem.* **27,** 927 (1990).

90JHC1313 W. Dostal, G. Heinisch, W. Holzer, I. Perhauc, and C. Zheng, *J. Heterocycl. Chem.* **27,** 1313 (1990).

90JHC1377 A. Turck, N. Plé, L. Mojovic, and G. Quéguiner, *J. Heterocycl. Chem.* **27,** 1377 (1990).

90JHC1645 N. Haider, G. Heinisch, and G. Kemetmüller, *J. Heterocycl. Chem.* **27,** 1645 (1990).

90JHC2125 M. J. Kornet, *J. Heterocycl. Chem.* **27,** 2125 (1990).

90JMC380 D. W. Combs, M. S. Rampulla, S. C. Bell, D. H. Klaubert, A. J. Tobia, R. Falotico, B. Haertlein, C. Lakas-Weiss, and J. B. Moore, *J. Med. Chem.* **33,** 380 (1990).

90JMC1591 L. Toma, G. Cignarella, D. Barlocco, and F. Ronchetti, *J. Med. Chem.* **33,** 1591 (1990).

90JMC1735 W. J. Coates, H. D. Prain, M. L. Reeves, and B. H. Warrington, *J. Med. Chem.* **33,** 1735 (1990).

90JMC2579 R. Bergmann, V. Eiermann, and R. Gericke, *J. Med. Chem.* **33,** 2579 (1990).

90JMC2870 A. Mertens, W. G. Friebe, B. Hüller-Beckmann, W. Kampe, L. Kling, and W. von der Saal, *J. Med. Chem.* **33,** 2870 (1990).

90JOC3410 R. J. Mattson and C. P. Sloan, *J. Org. Chem.* **55,** 3410 (1990).

90JOC5418 W. J. Coates and A. McKillop, *J. Org. Chem.* **55,** 5418 (1990).

90KGS960 I. V. Oleinik, O. A. Zagulyeva, A. Yu. Denisov, and V. P. Mamaev, *Khim. Geterotsikl. Soedin.,* 960 (1990).

90KGS1138 V. O. Kozminih, N. M. Igidov, E. N. Kozminih, and Yu. S. Andreichikov, *Khim. Geterotsikl. Soedin.,* 1138 (1990).

90KGS1244 E. G. Kovalev, G. L. Rusinov, V. A. Anufriev, and L. G. Egorova, *Khim. Geterotsikl. Soedin.,* 1244 (1990).

90KGS1691 E. G. Kovalev, V. A. Anufriev, and G. L. Rusinov, *Khim. Geterotsikl. Soedin.,* 1691 (1990).

90L1273 S. A. Chaffins, J. Y. Gui, C.-H. Lin, F. Lu, G. N. Salaita, D. A. Stern, and A. T. Hubbard, *Langmuir* **6,** 1273 (1990).

90LA293 S. A. S. Ghozlan, M. H. Mohamed, Y. Fakhr, and M. H. Elnagdi, *Liebigs Ann. Chem.,* 293 (1990).

90M565 B. D. Schober and T. Kappe, *Monatsh. Chem.* **121,** 565 (1990).

90MI1 S. Hagopian and S. L. Whittenburg, *J. Mol. Liq.* **45,** 273 (1990).

90MI2 R. Hazard, A. Tallec, R. Tardivel, J. J. Bourguignon, and C. G. Wermuth, *Electrochim. Acta* **35,** 1907 (1990).

90MI3 S. A. Essawy, *Delta J. Sci.* **14,** 477 (1990) [*CA* **117,** 191798 (1992)].
90MI5 S. Craddock, C. Purves, and D. W. H. Rankin, *J. Mol. Struct.* **220,** 193 (1990).
90MRC380 T. Liptaj, V. Konečný, and Š. Kováč, *Magn. Reson. Chem.* **28,** 380 (1990).
90PHA724 H. Horn, E. Morgenstern, and K. Unverferth, *Pharmazie* **45,** 724 (1990).
90PJC741 S. Bałoniak and A. Ostrowicz, *Pol. J. Chem.* **64,** 741 (1990).
90S467 Y. Kamitori, M. Hojo, R. Masuda, K. Kawasaki, S. Takata, and J. Ida, *Synthesis,* 467 (1990).
90S773 H. Dürr, H. Kilburg, and S. Bossmann, *Synthesis*, 773 (1990).
90SA(A)1087 L. Lapinski, J. Fulara, R. Czerminski, and M. J. Nowak, *Spectrochim. Acta, Part A* **46A,** 1087 (1990).
90SL227 L. Rodriguez, N. Lu, and N.-L. Yang, *Synlett*, 227 (1990).
90T6915 A. Štimac, B. Stanovnik, M. Tišler, and L. Golič, *Tetrahedron* **46,** 6915 (1990).
90TL6855 A. Meier and J. Sauer, *Tetrahedron Lett.* **31,** 6855 (1990).
90ZN(B)389 M. H. Elnagdi, F. A. M. Abdul-Aal, N. M. Taha, and Y. M. Yassin, *Z. Naturforsch., B* **45B,** 389 (1990).
90ZOR2022 V. V. Zalesov, N. A. Pulina, and Yu. S. Andreichikov, *Zh. Org. Khim.* **26,** 2022 (1990).
91AG1495 G. Maier, F. Fleischer, H.-O. Kalinowski, and R. Boese, *Angew. Chem* **103,** 1495 (1991).
91AKZ259 R. S. Vartanyan, A. L. Gyul'budagyan, and A. Kh. Khanamiryan, *Arm. Khim. Zh.* **44,** 259 (1991) [*CA* **116,** 59303 (1992)].
91AP455 E. Raviña, C. Teran, N. G. Dominguez, C. F. Masaguer, J. Gil-Longo, F. Orallo, and J. M. Calleja, *Arch. Pharm. (Weinheim, Ger.)* **324,** 455 (1991).
91AP853 M. H. Elnagdi and A. W. W. Erian, *Arch. Pharm. (Weinheim, Ger.)* **324,** 853 (1991).
91AP999 S. Corsano, G. Strappaghetti, R. Ferrini, and N. Giglioli, *Arch. Pharm. (Weinheim, Ger.)* **324,** 999 (1991).
91AX(C)1517 W. I. Jottier, H. L. De Winter, N. M. Blaton, O. M. Peeters, and C. J. De Ranter, *Acta Crystallogr., Sect. C* **C47,** 1517 (1991).
91AX(C)1933 A. J. Blake and D. W. H. Rankin, *Acta Crystallogr., Sect. C* **C47,** 1933 (1991).
91BCJ2032 E. A. Ghani, *Bull. Chem. Soc. Jpn.* **64,** 2032 (1991).
91CCC2251 G. Heinisch and W. Holzer, *Collect. Czech. Chem. Commun.* **56,** 2251 (1991).
91CJC972 G. Heinisch and W. Holzer, *Can. J. Chem.* **69,** 972 (1991).
91CL1953 Y. Nakamura and C.-G. Shin, *Chem. Lett.*, 1953 (1991).
91CPB352 Y. Nomoto, H. Takai, T. Ohno, and K. Kubo, *Chem. Pharm. Bull.* **39,** 352 (1991).
91FA873 G. Ciciani, V. Dal Piaz, and M. P. Giovannoni, *Farmaco* **46,** 873 (1991).
91H1173 V. Dal Piaz, G. Ciciani, and M. P. Giovannoni, *Heterocycles* **32,** 1173 (1991).
91H1387 T. Sakamoto, N. Funami, Y. Kondo, and H. Yamanaka, *Heterocycles* **32,** 1387 (1991).

91IJC(B)932 H. V. Patel, S. P. Pandey, P. S. Fernandes, and K. A. Vyas, *Indian J. Chem., Sect. B* **30B,** 932 (1991).

91JA7342 Y. Ikeura, K. Kurihara, and T. Kumitake, *J. Am. Chem. Soc.* **113,** 7342 (1991).

91JAN249 O. D. Hensens, R. P. Borris, L. R. Koupal, C. G. Caldwell, S. A. Currie, A. A. Haidri, C. F. Homnick, S. S. Honeycutt, S. M. Lindenmayer, C. D. Schwartz, B. A. Weissberger, H. B. Woodruff, D. L. Zink, L. Zitano, J. M. Fieldhouse, T. Rollins, M. S. Springer, and J. P. Springer, *J. Antibiot.* **44,** 249 (1991).

91JCS(P1)991 T. Yamasaki, E. Kawaminami, T. Yamada, T. Okawara, and M. Furukawa, *J. Chem. Soc., Perkin Trans. 1,* 991 (1991).

91JCS(P1)3361 G. Ferguson, A. J. Lough, D. Mackay, and G. Weeratunga, *J. Chem. Soc., Perkin Trans. 1,* 3361 (1991).

91JHC385 S. J. Choi, S. C. Shin, and Y.-J. Yoon, *J. Heterocycl. Chem.* **28,** 385 (1991).

91JHC583 J. G. Samaritoni and G. Babbitt, *J. Heterocycl. Chem.* **28,** 583 (1991).

91JHC1043 J.-P. Vors, *J. Heterocycl. Chem.* **28,** 1043 (1991).

91JHC1189 M. Hahn, G. Heinisch, W. Holzer, and H. Schwarz, *J. Heterocycl. Chem.* **28,** 1189 (1991).

91JHC1235 S.-Y. Choi, S.-G. Lee, and Y.-J. Yoon, *J. Heterocycl. Chem.* **28,** 1235 (1991).

91JHC1441 N. Haider, G. Heinisch, and R. Wanko, *J. Heterocycl. Chem.* **28,** 1441 (1991).

91JHC2079 S.-Y. Choi, S. C. Shin, and Y.-J. Yoon, *J. Heterocycl. Chem.* **28,** 2079 (1991).

91JOC1963 F. F. Owings, M. Fox, C. J. Kowalski, and N. H. Baine, *J. Org.Chem.* **56,** 1963 (1991).

91JPC2404 M. J. Nowak, L. Lapinski, J. Fulara, A. Leš, and L. Adamowicz, *J. Phys. Chem.* **95,** 2404 (1991).

91KGS783 R. S. Vartanyan, A. L. Gyulbudagyan, A. Kh. Khanamiryan, E. N. Mkrtumyan, and Zh. V. Kazaryan, *Khim. Geterotsikl. Sooedin.*, 783 (1991).

91KGS1545 E. G. Kovalev, G. L. Kusinov, G. G. Aleksandrov, V. A. Anufriev, E. O. Sidorov, and A. I. Chernyshev, *Khim. Geterotsikl. Soedin.*, 1545 (1991).

91LA1225 A. Deeb, H. Sterk, and T. Kappe, *Liebigs Ann. Chem.,* 1225 (1991).

91M1055 G. Heinisch, W. Holzer, and T. Huber, *Monatsh. Chem.* **122,** 1055 (1991).

91MI1 P. Coudert, E. Duroux, P. Bastide, J. Couquelet, and P. Tronche, *J. Pharm. Belg.* **46,** 375 (1991).

91MI2 G. Heinisch and E. Pittauer, *Sci. Pharm.* **59,** 111 (1991).

91MI3 A. A. Ismail, R. Radwan, H. A. A. Hamid, G. H. Sayed, and S. M. Mohamed, *J. Chem. Soc. Pak.* **13,** 111 (1991).

91MI4 F. A. Yassin, A. F. El-Farargy, M. M. El-Mobayed, M. Y. El-Kady, and M. R. A. El-Maksoud, *J. Chem. Soc. Pak.* **13,** 267 (1991).

91MI5 A. S. M. Gommaa and M. Al Selhdar, *Alexandria J. Pharm. Sci.* **5,** 216 (1991) [*CA* **116,** 174707 (1992)].

91MI6 S. L. Srivastava and G. R. A. Rohitashava, *Acta Cienc. Indica,* [*Ser.*] *Phys.* **17P,** 177 (1991) [*CA* **117,** 16276 (1992)].

91MI7 M. H. Palmer and I. C. Walker, *Chem. Phys.* **157,** 187 (1991).

91MI8 R. Goeschke, J. Gainer, G. A. Howarth, R. B. Wallis, R. Kerry, J. Ambler, V. S. Findlay, and K. D. Butler, *Eur. J. Med. Chem.* **26,** 715 (1991).

91MI9 E. Kasztreiner, K. Czakó, J. Kosáry, E. Diesler, G. Rabloczky, J. Jaszlitz, and A. Jednákovits, *Eur. J. Med. Chem.* **26,** 739 (1991).

91OMS595 E. Pittenauer, G. Allmaier, E. R. Schmid, W. Stanek, and G. Heinisch, *Org. Mass Spectrom.* **26,** 595 (1991).

91OMS1082 J.-L. Chabard, J. Taoufik, J. Couquelet, and P. Tronche, *Org. Mass Spectrom.* **26,** 1082 (1991).

91OPP645 G. H. Elgemeie, S. R. El-Ezbawy, M. M. Ramiz, and O. A. Mansour, *Org. Prep. Proced. Int.* **23,** 645 (1991).

91OPP760 K. G. Peterman and W. Dmowski, *Org. Prep. Proced. Int.* **23,** 760 (1991).

91PJC1085 S. Bałoniak and A. Ostrowicz, *Pol. J. Chem.* **65,** 1085 (1991).

91PS(56)81 F. A. Khalifa, *Phosphorus Sulfur* **56,** 81 (1991).

91PS(59)243 J. Nakayama, R. Hasemi, and F. Iwasaki, *Phosphorus Sulfur* **59,** 243 (1991).

91RCM421 E. Pittenauer, G. Allmaier, E. R. Schmid, P. Krenmayr, and G. Heinisch, *Rapid Commun. Mass Spectrom.* **5,** 421 (1991).

91RRC399 I. Motoc and O. E. Polansky, *Rev. Roum. Chim.* **36,** 399 (1991).

91RRC657 M. Caprosu, E. Stefanescu, M. Ungureanu, and M. Petrovanu, *Rev. Roum. Chim.* **36,** 657 (1991).

91SC271 Z. Moussavi, P. Depreux, and D. Lesieur, *Synth. Commun.* **21,** 271 (1991).

91SC1021 H. V. Patel, K. A. Vyas, S. P. Pandey, F. Tavares, and P. S. Fernandes, *Synth. Commun.* **21,** 1021 (1991).

91SC1935 H. V. Patel, K. A. Vyas, S. P. Pandey, F. Tavares, and P. S. Fernandes, *Synth. Commun.* **21,** 1935 (1991).

91T6231 H. Uno, S.-I. Okada, and H. Suzuki, *Tetrahedron* **47,** 6231 (1991).

91T6251 Q. Meng and M. Hesse, *Tetrahedron* **47,** 6251 (1991).

91T8573 N. Haider, G. Heinisch, and J. Moshuber, *Tetrahedron* **47,** 8573 (1991).

91TL57 G. Maier and F. Fleischer, *Tetrahedron Lett.* **32,** 57 (1991).

91TL5949 L. Baumann and G. Seitz, *Tetrahedron Lett.* **32,** 5949 (1991).

91ZN(B)1720 M. F. Ismail, F. S. Sayed, S. A. Emara, and A. A. Shindy, *Z. Naturforsch., B* **B46,** 1720 (1991).

91ZOR1105 N. K. Genkina, V. V. Ipatkin, and L. N. Kurkovskaya, *Zh. Org.Khim.* **27,** 1105 (1991).

91ZOR1123 V. V. Kuzmenko, A. V. Gulevskaya, and A. F. Pozharskii, *Zh. Org. Khim.* **27,** 1123 (1991).

92AP119 N. Haider, G. Heinisch, and J. Moshuber, *Arch. Pharm. (Weinheim, Ger.)* **325,** 119 (1992).

92API87 S. Corsano, G. Strappaghetti, R. Scapicchi, and V. Anania, *Arch. Pharm. (Weinheim, Ger.)* **325,** 187 (1992).

92AX(C)1504 M. Ratajczak-Sitarz and A. Katrusiak, *Acta Crystallogr., Sect. C* **C48,** 1504 (1992).

92BCJ2894 Y. Nakashima, H. Kanada, M. Fukunaga, K. Suzuki, and K. Takahashi, *Bull. Chem. Soc. Jpn.* **65,** 2894 (1992).

92CB1227 R. Munschauer and G. Maas, *Chem. Ber.* **125,** 1227 (1992).

92CCC1758 R. M. Mohareb and N. I. Abdel-Sayed, *Collect. Czech. Chem.Commun.* **57,** 1758 (1992).

92CCC1951 M. L. Iskander, S. A. El-Abbady, A. A. Shalaby, and A. H. Moustafa, *Collect. Czech. Chem. Commun.* **57,** 1951 (1992).

92CJC1886 L. Chen, L. K. Thompson, and J. N. Bridson, *Can. J. Chem.* **70,** 1886 (1992).

92CJC2709 L. Chen, L. K. Thompson, and J. N. Bridson, *Can. J. Chem.* **70,** 2709 (1992).

92CPL(189)560 M. Terazima and N. Hirota, *Chem. Phys. Lett.* **189,** 560 (1992).

92CPL(197)59 T. D. Bouman and A. E. Hansen, *Chem. Phys. Lett.* **197,** 59 (1992).

92FA37 P. Coudert, C. Rubat, E. Duroux, P. Bastide, J. D. Couquelet, P. Tronche, and E. Albuisson, *Farmaco* **47,** 37 (1992).

92G41 R. M. Mohareb, H. Z. Shams, and M. H. Elnagdi, *Gazz. Chim. Ital.* **122,** 41 (1992).

92G503 R. M. Mohareb, A. M. El-Torgoman, S. I. Aziz, S. M. El-Kousy, and M. Riad, *Gazz. Chim. Ital.* **122,** 503 (1992).

92H225 S. Konno, M. Sagi, F. Siga, and M. Yamanaka, *Heterocycles* **34,** 225 (1992).

92H1183 T. Itoh, M. Okada, K. Nagata, and A. Ohsawa, *Heterocycles* **34,** 1183 (1992).

92H1507 Y. Uchibori, M. Umeno, and H. Yoshioka, *Heterocycles* **34,** 1507 (1992).

92H1631 V. G. S. Box, *Heterocycles* **34,** 1631 (1992).

92IJC(B)273 H. V. Patel, K. A. Vyas, S. P. Pandey, F. Tavares, and P. S. Fernandes, *Indian J. Chem., Sect. B* **31B,** 273 (1992).

92JA1838 S. Prathapan, K. E. Robinson, and W. C. Agosta, *J. Am. Chem. Soc.* **114,** 1838 (1992).

92JAN1723 T. Ogita, A. Sato, R. Enokita, K. Suzuki, M. Ishii, T. Negishi, T. Okazaki, K. Tamaki, and K. Tanzawa, *J. Antibiot.* **45,** 1723 (1992).

92JCR(S)176 S. Robert-Piessard, G. Le Baut, J. M. Robert, J. M. Leger, and M. Saux, *J. Chem. Res., Synop.,* 176 (1992).

92JCS(CC)1186 U. Schmidt and B. Riedl, *J. Chem. Soc., Chem.Commun.,* 1186 (1992).

92JCS(P1)409 J. R. Russell, C. D. Garner, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1,* 409 (1992).

92JHC87 S. Mataka, O. Misumi, W. H. Lin, M. Tashiro, K. Takahashi, and A. Torii, *J. Heterocycl. Chem.* **29,** 87 (1992).

92JHC93 N. Klempier, A. de Raadt, H. Griengl, and G. Heinisch, *J. Heterocycl. Chem.* **29,** 93 (1992).

92JHC825 T. Yamasaki, E. Kawaminami, F. Uchimura, Y. Okamoto, T. Okawara, and M. Furukawa, *J. Heterocycl. Chem.* **29,** 825 (1992).

92JHC935 J. E. Gready, P. M. Hatton, and S. Sternhell, *J. Heterocycl. Chem.* **29,** 935 (1992).

92JHC1583 A. E. Mourad, D. S. Wise, and L. B. Townsend, *J. Heterocycl. Chem.* **29,** 1583 (1992).

92JMC3288 J. Easmon, G. Heinisch, W. Holzer, and B. Rosenwirth, *J. Med. Chem.* **35,** 3288 (1992).

92JMC4092 A. Melikian, G. Schlewer, J.-P. Chambon, and C. G. Wermuth, *J. Med. Chem.* **35,** 4092 (1992).

92JOC542 H. Tsukube, H. Minatogawa, M. Munakata, M. Toda, and K. Matsumoto, *J. Org. Chem.* **57,** 542 (1992).

92JOC1585 G. A. Olah, M. B. Sassaman, M. Zuanic, C. B. Rao, G. K. S. Prakash, R. Gilardi, J. Flippen-Anderson, and C. George, *J. Org. Chem.* **57,** 1585 (1992).

92JOC3257 J. M. Sitamze, M. Schmitt, and C. G. Wermuth, *J. Org. Chem.* **57,** 3257 (1992).

92JPC6250 L. Lapinski, M. J. Nowak, J. Fulara, A. Leš, and L. Adamowicz, *J. Phys. Chem.* **96,** 6250 (1992).

92JPC9204 M. Fulscher, K. Andersson, and B. O. Roos, *J. Phys. Chem.* **96,** 9204 (1992).

92JPS836 A. Chauvet, J. Masse, J.-P. Ribet, D. Bigg, J.-M. Autin, J.-L. Maurel, J.-F. Patoiseau, and J. Jaud, *J. Pharm. Sci.* **81,** 836 (1992).

92JSP215 J. G. Philis, *J. Mol. Spectrosc.* **155,** 215 (1992).

92LA19 G. Heinisch and T. Huber, *Liebigs Ann. Chem.*, 19 (1992).

92LA547 J. Lange, J. Karolak-Wojciechowska, and H. Tondys, *Liebigs Ann. Chem.*, 547 (1992).

92LA777 M. P. Matia, J. L. García-Navio, J. J. Vaquero, and J. Alvarez-Builla, *Liebigs Ann. Chem.*, 777 (1992).

92MI1 H. R. Kricheldorf and P. Jahnke, *Polym. Bull.* **28,** 411 (1992).

92MI2 M. G. Marei and M. M. Mishrikey, *J. Chem. Soc. Pak.* **14,** 66 (1992).

92MI3 G. H. Sayed, N. M. Yousif, S. A. Shiba, S. M. Mohamed, and I. M. Flefel, *J. Chem. Soc. Pak.* **14,** 125 (1992).

92MI4 G. H. Sayed, S. A. Shiba, A. Radwan, S. M. Mohamed, and M. Khalil, *Chin. J. Chem.* **10,** 475 (1992) [*CA* **119,** 8756 (1993)].

92MI5 J. C. Del Valle and J. L. G. De Paz, *J. Mol. Struct. (Theochem.)* **86,** 481 (1992) [*CA* **116,** 193373 (1992)].

92MI6 C. K. Kim, B. S. Lee, and I. Lee, *Bull. Korean Chem. Soc.* **13,** 32 (1992).

92MI7 P. Mátyus, J. Kosáry, E. Kasztreiner, N. Makk, E. Diesler, K. Csakó, G. Rabloczky, L. Jaszlits, E. Horváth, Z. Tömösközi, G. Cseh, E. Horváth, and P. Arányi, *Eur. J. Med. Chem.* **27,** 107 (1992).

92MI8 S. Corsano, G. Strappaghetti, A. Codagnone, R. Scapicchi, and G. Marucci, *Eur. J. Med. Chem.* **27,** 545 (1992).

92OS79 D. L. Boger, J. S. Panek, and M. Patel, *Org. Synth.* **70,** 79 (1992).

92PHA249 M. J. Kane, E. W. Huber, F. P. Miller, and J. H. Kehne, *Pharmazie* **47,** 249 (1992).

92PHA418 A. A. Elagamey, F. M. A. El-Taweel, and M. N. M. Khodeir, *Pharmazie* **47,** 418 (1992).

92PHA679 N. Haider, G. Heinisch, and J. Moshuber, *Pharmazie* **47,** 679 (1992).

92PHA792 L. I. Ibrahim, S. M. Eldin, and F. A. Attaby, *Pharmazie* **47,** 792 (1992).

92PJC935 S. Bałoniak and A. Ostrowicz, *Pol. J. Chem.* **66,** 935 (1992).

92PJC1015 M. L. Iskander, S. A. El-Abbady, A. A. Shalaby, and A. H. Moustafa, *Pol. J. Chem.* **66,** 1015 (1992).

92PS299 M. A. El-Hashash, F. M. Soliman, M. S. Amine, and M. Morsi, *Phosphorus Sulfur* **69,** 299 (1992).

92RRC819 R. Bacaloglu, I. Bacaloglu, and Z. Simon, *Rev. Roum. Chim.* **37,** 819 (1992).

92SC787 K. Matsumoto, S. Hashimoto, M. Hashimoto, M. Toda, and S. Otani, *Synth. Commun.* **22,** 787 (1992).
92T335 C. W. Bird, *Tetrahedron* **48,** 335 (1992).
92T7857 C. W. Bird, *Tetrahedron* **48,** 7857 (1992).
92TL4787 A. Ostrowicz, S. Bałoniak, M. Makosza, and A. Rykowski, *Tetrahedron Lett.* **33,** 4787 (1992).
92TL7331 K. Banert, M. Hagedorn, and D. Alder, *Tetrahedron Lett.* **33,** 7331 (1992).
92TL7345 H. Amri, M. M. El Gaied, T. Ben Ayed, and J. Villieras, *Tetrahedron Lett.* **33,** 7345 (1992).
92TL7613 K. J. Hale, V. M. Delisser, and S. Manaviazar, *Tetrahedron Lett.* **33,** 7613 (1992).
92TL8019 T. Hierstetter, B. Tischler, and J. Sauer, *Tetrahedron Lett.* **33,** 8019 (1992).
92ZOB2100 I. F. Tupitsyn, A. S. Popov, and A. Yu. Shibaev, *Zh. Obshch. Khim.* **62,** 2100 (1992).
92ZOB2319 I. F. Tupitsyn, A. S. Popov, and A. Yu. Shibaev, *Zh. Obshch. Khim.* **62,** 2319 (1992).
93ACS95 M. Woźniak and H. C. van der Plas, *Acta Chem. Scand.* **47,** 95 (1993).
93AP39 M. J. Mokrosz, *Arch. Pharm. (Weinheim, Ger.)* **326,** 39 (1993).
93AX(C)36 A. Katrusiak, *Acta Crystallogr., Sect. C* **C49,** 36 (1993).
93BCJ477 G. H. Sayed, A. Radwan, A. A. Hamed, and W. E.-S. Boraie, *Bull.Chem. Soc. Jpn.* **66,** 477 (1993).
93BCJ1722 F. M. Abdelrazek and A. M. Salah, *Bull. Chem. Soc. Jpn.* **66,** 1722 (1993).
93BMC2713 S. Corsano, G. Strappaghetti, R. Scapicchi, and O. Scalise, *Bioorg. Med. Chem. Lett.* **3,** 2713 (1993).
93BSF488 A. Turck, N. Plé, L. Mojovic, and G. Quéguiner, *Bull. Soc. Chim. Fr.* **130,** 488 (1993).
93CCC1925 S. Yassin, A.-E. H. A. El-Aleem, I. E. El-Sayed, and A. I. Hashem, *Collect. Czech. Chem. Commun.* **58,** 1925 (1993).
93CJC1086 L. Chen, L. K. Thompson, and J. N. Bridson, *Can. J. Chem.* **71,** 1086 (1993).
93CL509 T. Fukuhara and N. Yoneda, *Chem. Lett.*, 509 (1993).
93CPB156 A. Kuno, H. Sakai, Y. Sugiyama, and H. Takasugi, *Chem. Pharm. Bull.* **41,** 156 (1993).
93FA1427 M. L. Carmellino, G. Massolini, G. Pagani, F. Zani, and G. Leri, *Farmaco* **48,** 1427 (1993).
93H219 K.-J. Hwang and K.-H. Park, *Heterocycles* **36,** 219 (1993).
93H519 E. Zára-Kaczián and P. Mátyus, *Heterocycles* **36,** 519 (1993).
93H785 P. Mátyus, K. Csakó, A. Behr, I. Varga, B. Podányi, M. von Arnim, and P. Várkonyi, *Heterocycles* **36,** 785 (1993).
93H909 M. Takahashi, H. Kotashima, and T. Saitoh, *Heterocycles* **35,** 909 (1993).
93H1313 W. J. Coates and A. McKillop, *Heterocycles* **35,** 1313 (1993).
93IC4063 L. Chen, L. K. Thompson, S. S. Tandon, and J. N. Bridson, *Inorg. Chem.* **32,** 4063 (1993).
93IJC(B)662 S. P. Hiremath, A. S. Jivanagi, and M. G. Purohit, *Indian J. Chem., Sect. B* **32B,** 662 (1993).

93IZV539 A. Kh. Khanamiryan, A. L. Gyulbudagyan, P. S. Vartanyan, M. Kh. Dzhafarov, and Yu. T. Struchkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 539 (1993) [*CA* **124,** 55888 (1996)].

93JA1353 J. Cioslowski, J. Sauer, J. Hetzenegger, T. Karcher, and T. Hierstetter, *J. Am. Chem. Soc.* **115,** 1353 (1993).

93JA3828 E. J. Corey, M. C. Noe, and S. Sarchar, *J. Am. Chem. Soc.* **115,** 3828 (1993).

93JA4925 T. A. Zona and J. L. Goodman, *J. Am. Chem. Soc.* **115,** 4925 (1993).

93JA8457 H. H. Wasserman, R. W. DeSimone, D. L. Boger, and C. M. Baldino, *J. Am. Chem. Soc.* **115,** 8457 (1993).

93JA11906 J. C. Tai L. Yang, and N. L. Allinger, *J. Am. Chem. Soc.* **115,** 11906 (1993).

93JA12579 E. J. Corey and M. C. Noe, *J. Am. Chem. Soc.* **115,** 12579 (1993).

93JAN921 Y. Nishiyama K. Sugawara, K. Tomita, H. Yamamoto, H. Kamei, and T. Oki, *J. Antibiot.* **46,** 921 (1993).

93JAN928 K. Sugawara, S. Toda, T. Moriyama, M. Konishi, and T. Oki, *J. Antibiot.* **46,** 928 (1993).

93JAN1658 M. Ueno, M. Amemiya, T. Someno, T. Masuda, H. Iinuma, H. Naganawa, M. Hamada, M. Ishizuka, and T. Takeuchi, *J. Antibiot.* **46,** 1658 (1993).

93JCR(S)358 A. H. H. Elghandour, *J. Chem. Res. Synop.*, 358 (1993).

93JCS(CC)1179 I. H. Aspinall, P. M. Cowley, G. Mitchell, and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1179 (1993).

93JCS(P1)1931 M. Vinnikova, D. Gertner, S. Cohen, and A. Zilkha, *J. Chem. Soc., Perkin Trans. 1*, 1931 (1993).

93JCS(P2)331 N. A. Burton, D. V. S. Green, I. H. Hillier, P. J. Taylor, M. A. Vincent, and S. Woodcock, *J. Chem. Soc., Perkin Trans. 2*, 331 (1993).

93JHC865 W. Holzer and G. Seiringer, *J. Heterocycl. Chem.* **30,** 865 (1993).

93JHC1093 P. Coudert, J. Couquelet, P. Tronche, and F. Leal, *J. Heterocycl. Chem.* **30,** 1093 (1993).

93JHC1501 S. G. Hegde and C. R. Jones, *J. Heterocycl. Chem.* **30,** 1501 (1993).

93JHC1685 G. Heinisch and T. Langer, *J. Heterocycl. Chem.* **30,** 1685 (1993).

93JOC633 G. V. Lamoureux and G. M. Whitesides, *J. Org. Chem.* **58,** 633 (1993).

93JOM229 G. Menchi, S. Paganelli, U. Matteoli, A. Scrivanti, and C. Botteghi, *J. Organomet. Chem.* **450,** 229 (1993).

93JPC1356 A. R. Bérces, P. G. Szalay, I. Magdó, G. Fogarasi, and G. Pongor, *J. Phys. Chem.* **97,** 1356 (1993).

93KGS202 M. A. Mikhaleva, I. I. Naumenko, and V. P. Mamaev, *Khim. Geterotsikl. Soedin.*, 202 (1993).

93MC58 V. V. Semenov, S. A. Shevelev, and L. G. Mel'nikova, *Mendeleev Commun.*, 58 (1993) [*CA* **119,** 138553 (1993)].

93MI1 J. Easmon, G. Heinisch, and W. Holzer, *Sci. Pharm.* **61,** 3 (1993).

93MI2 M. Toda, H. Tsukube, H. Minatogawa, M. Munakata, K. Hirotsu, I. Miyahara, T. Higuchi, and K. Matsumoto, *Supromol. Chem.* **2,** 289 (1993).

93MI3 S. Mohan and R. Murugan, *Indian J. Pure Appl. Phys.* **31,** 496 (1993).

93MI4 R. Jonas, M. Klockow, I. Lues, H. Prücher, H. J. Schliep, and H. Wurziger, *Eur. J. Med. Chem.* **28,** 129 (1993).

93MI5 R. Jonas, H. Prücher, and H. Wurziger, *Eur. J. Med. Chem.* **28,** 141 (1993).

93MI6 S. Corsano, R. Scapicchi, G. Strappaghetti, G. Marucci, and F. Paparelli, *Eur. J. Med. Chem.* **28,** 647 (1993).

93MI7 D. Dorohoi and V. Holban, *J. Mol. Struct.* **293,** 133 (1993).

93OPP293 A. H. H. Elghandour, M. K. A. Ibrahim, I. S. A. Hafiz, and M. H. Elnagdi, *Org. Prep. Proced. Int.* **25,** 293 (1993).

93QSAR146 L. Caruso, G. Musumarra, and A. R. Katritzky, *Quant. Struct. Act. Relat. Pharmacol. Chem. Biol.* **12,** 146 (1993).

93RRC213 M. El-Mobayed, G. H. Sayed, A. G. El-Shekeil, and E. Abdel Ghani, *Rev. Roum. Chim.* **38,** 213 (1993).

93RRC759 M. Petrovanu, C. Anton, D. Dorohoi, M. Caproşu, and I. Fulger, *Rev. Roum. Chim.* **38,** 759 (1993).

93RRC989 M. G. Marei and M. M. Mishrikey, *Rev. Roum. Chim.* **38,** 989 (1993).

93RRC1223 S. A. Essawy, A. A. El-Sawy, M. Y. El-Kady, and A. A. F. Wasfy, *Rev. Roum. Chim.* **38,** 1223 (1993).

93S334 W. J. Coates and A. McKillop, *Synthesis*, 334 (1993).

93S809 U. Schmidt and B. Riedl, *Synthesis*, 809 (1993).

93SC1371 J. Lange, H. Tondys, W. Koberda, and M. Gniewosz, *Synth. Commun.* **23,** 1371 (1993).

93T599 A. Turck, N. Plé, B. Ndzi, G. Quéguiner, N. Haider, H. Schuller, and G. Heinisch, *Tetrahedron* **49,** 599 (1993).

93T8605 F. P. J. T. Rutjes, N. M. Teerhuis, H. Hiemstra, and W. N. Speckamp, *Tetrahedron* **49,** 8605 (1993).

93TL161 V. Dal Piaz, M. P. Giovannoni, G. Ciciani, D. Giomi, and R. Nesi, *Tetrahedron Lett.* **34,** 161 (1993).

93TL683 K. Tamaki, T. Ogita, K. Tanzawa, and Y. Sugimura, *Tetrahedron Lett.* **34,** 683 (1993).

93TL3777 P. G. Baraldi, S. Manfredini, D. Simoni, and G. Spalluto, *Tetrahedron Lett.* **34,** 3777 (1993).

93TL3903 V. Dal Piaz, M. P. Giovannoni, and G. Ciciani, *Tetrahedron Lett.* **34,** 3903 (1993).

93TL5135 Y. Kamitori, M. Hojo, R. Masuda, T. Ikemura, and Y. Mori, *Tetrahedron Lett.* **34,** 5135 (1993).

93TL8477 K. Tamaki, S. Kurihara, and Y. Sugimura, *Tetrahedron Lett.* **34,** 8477 (1993).

93ZOR911 V. N. Lisitsyn, S. A. H. Omar, and S. N. Krasnokutskii, *Zh. Org. Khim.* **29,** 911 (1993).

94AG1733 H. Bockholt, J. M. Beale, and J. Rohr, *Angew. Chem.* **106,** 1733 (1994).

94AG2432 P. N. W. Baxter, J.-M. Lehn, J. Fischer, and M.-T. Youinou, *Angew. Chem.* **106,** 2432 (1994).

94AP365 M. Richter and G. Seitz, *Arch. Pharm. (Weinheim, Ger.)* **327,** 365 (1994).

94AX(B)68 K. Prout, K. Burns, and A. M. Roe, *Acta Crystallogr., Sect. B* **B50,** 68 (1994).

94AX(B)71 K. Prout, C. Bannister, K. Burns, M. Chen, B. H. Warrington, and J. G. Vinter, *Acta Crystallogr., Sect. B* **B50,** 71 (1994).

94AX(C)1150 O. Simonsen, E. Fanghänel, B. Brummerstedt Iversen, and F. Krebs Larsen, *Acta Crystallogr., Sect. C* **C50,** 1150 (1994).

94CCC186 G. A. M. Nawwar, R. H. Swellem, and L. M. Chabaka, *Collect. Czech. Chem. Commun.* **59,** 186 (1994).

94CPB371 M. Morishita, J. Kobayashi, H. Yamada, and T. Yajima, *Chem. Pharm. Bull.* **42,** 371 (1994).

94CPB1609 T. Seki, T. Takezaki, R. Ohuchi, H. Ohuyabu, T. Ishimori, and K.Yasuda, *Chem. Pharm. Bull.* **42,** 1609 (1994).

94CPB1768 T. Itoh, H. Hasegawa, K. Nagata, Y. Matsuya, M. Okada, and A. Ohsawa, *Chem. Pharm. Bull.* **42,** 1768 (1994).

94H(37)171 P. Mátyus, K. Fuji, and K. Tanaka, *Heterocycles* **37,** 171 (1994).

94H(37)249 C. W. Bird, *Heterocycles* **37,** 249 (1994).

94H(37)401 M. Khodja, D. Sicker, and H. Wilde, *Heterocycles* **37,** 401 (1994).

94H(37)709 T. Itoh, H. Hasegawa, K. Nagata, Y. Matsuya, and A. Ohsawa, *Heterocycles* **37,** 709 (1994).

94H(37)2149 A. Turck, N. Plé, and G. Quéguiner, *Heterocycles* **37,** 2149 (1994).

94H(38)125 N. Haider, G. Heinisch, and J. Moshuber, *Heterocycles* **38,** 125 (1994).

94H(38)1273 D. Toussaint, J. Suffert, and C.-G. Wermuth, *Heterocycles* **38,** 1273 (1994).

94H(38)1957 P. Mátyus, K. Fuji, K. Tanaka, J. Rohonczy, R. Hargitai, and P. Sohár, *Heterocycles* **38,** 1957 (1994).

94H(38)2081 G. Heinisch, B. Matuszczak, and K. Mereiter, *Heterocycles* **38,** 2081 (1994).

94H(38)2695 H. G. Krug, R. Neidlein, C. Krieger, and W. Kramer, *Heterocycles* **38,** 2695 (1994).

94H(39)271 J. M. Sitamzé, A. Mann, and C.-G. Wermuth, *Heterocycles* **39,** 271 (1994).

94JAN1473 H. Haruyama, Y. Ohkuma, H. Nagaki, T. Ogita, K. Tamaki, and T. Kinoshita, *J. Antibiot.* **47,** 1473 (1994).

94JAN1481 K. Tamaki S. Kurihara, T. Oikawa, K. Tanzawa, and Y. Sugimura, *J. Antibiot.* **47,** 1481 (1994).

94JCP419 D. Dorohoi, H. Partenie, L. Chiran, and C. Anton, *J. Chem. Phys.* **91,** 419 (1994).

94JCR(S)4 F. Arnaud-Neu, J.-J. Bourguignon, S. K. Mehta, and C. G. Wermuth, *J. Chem. Res. Synop.*, 4 (1994).

94JCS(CC)487 S. Brooker, R. J. Kelly, and G. M. Sheldrick, *J. Chem. Soc., Chem. Commun.*, 487 (1994).

94JCS(CC)1867 M. A. Ciufolini and N. Xi, *J. Chem. Soc., Chem. Commun.*, 1867 (1994).

94JCS(P2)199 P. W. Kenny, *J. Chem. Soc., Perkin Trans. 2*, 199 (1994).

94JHC967 M. J. Kornet, K. A.-N. Ali, and M. I. Steinberg, *J. Heterocycl.Chem.* **31,** 967 (1994).

94JHC1199 S.-D. Cho, J.-W. Chung, W.-Y. Choi, S.-K. Kim, and Y.-J. Yoon, *J. Heterocycl. Chem.* **31,** 1199 (1994).

94JIC195 N. R. Singh, N. R. Singh, and W. B. Singh, *J. Indian Chem. Soc.* **71,** 195 (1994).

94JPO743 D. E. Leahy, J. J. Morris, P. J. Taylor, and A. R. Wait, *J. Phys. Org. Chem.* **7,** 743 (1994).

94M1437 M. S. Abd El Halim, A. Nada, and W. A. Gad, *Monatsh. Chem.* **125,** 1437 (1994).

94MI1 M. Bruma, B. Schulz, and F. W. Mercer, *Polymer* **35,** 4209 (1994).

94MI2 G. H. Sayed, A. Radwan, M. S. A. Elhalim, and M. Khalil, *J. Chem. Soc. Pak.* **16,** 265 (1994).

94MI3 P. G. Baraldi, G. Spalluto, S. Manfredini, and D. Simoni, *Acta Chim. Slovenica* **41,** 149 (1994).

94MI4 T. Kappe, *Acta Chim. Slovenica* **41,** 219 (1994).

94MI5 D. Toussaint, J. Suffert, and C. G. Wermuth, *Acta Chim. Slovenica* **41,** 253 (1994).

94MI6 A. Hichliffe, M. Soscun, and J. Humberto, *J. Mol. Struct. (Theochem.)* **110,** 109 (1994).

94MI7 H. Shimada, A. Uehara, F. Shimizu, H. Kawano, Y. Nibu, and R. Shimada, *Fukuoka Daigaku Rigaku Shuho* **24,** 99 (1994) [*CA* **122,** 186816 (1995)].

94MI8 V. Dal Piaz, M. P. Giovannoni, R. Laguna, and E. Cano, *Eur. J. Med. Chem.* **29,** 249 (1994).

94MI9 P. Coudert, E. Albuisson, J. Y. Boire, E. Duroux, P. Bastide, and J. Couquelet, *Eur. J. Med. Chem.* **29,** 471 (1994).

94MI10 M. E. Castro, E. Rosa, J. A. Osuna, T. Garcia-Ferreiro, M. Loza, M. I. Cadavid, J. A. Fontenla, C. F. Masaguer, J. Cid, E. Raviña, G. García-Mera, J. Rodriguez, and M. L. de Ceballos, *Eur. J. Med. Chem.* **29,** 831 (1994).

94MP557 E. F. Archibong and A. J. Thakkar, *Mol. Phys.* **81,** 557 (1994).

94NJC643 R. Brettle, D. A. Dunmur, C. M. Marson, and M. Pinol, *New J. Chem.* **18,** 643 (1994).

94PHA575 N. Haider, G. Heinisch, and J. Moshuber, *Pharmazie* **49,** 575 (1994).

94PJC255 M. Ratajczak-Sitarz and A. Katrusiak, *Pol. J. Chem.* **68,** 255 (1994).

94PS(86)203 M. S. Abbady and S. M. Radwan, *Phosphorus Sulfur* **86,** 203 (1994).

94PS(88)147 A. H. H. Elghandour, M. K. A. Ibrahim, B. El-Badry, and H. K. Waly, *Phosphorus Sulfur* **88,** 147 (1994).

94PS(91)9 R. Popescu, V. Mureşan, Z. Moldovan, and M. Culea, *Phosphorus Sulfur* **91,** 9 (1994).

94RRC991 V. E. Sahini, E. Constantinescu, S. Cilianu, M. Hillebrand, E. Volanschi, C. Bendic, G. Sala, and M. Andrei, *Rev. Roum. Chim.* **39,** 991 (1994).

94S66 D. Enders, O. Meyer, G. Raabe, and J. Runsink, *Synthesis*, 66 (1994).

94S669 V. Dal Piaz, G. Ciciani, and M. P. Giovannoni, *Synthesis*, 669 (1994).

94S1158 P. G. Baraldi, A. Bigoni, B. Cacciari, C. Caldari, S. Manfredini, and G. Spalluto, *Synthesis*, 1158 (1994).

94SC773 G. Heinisch and T. Langer, *Synth. Commun.* **24,** 773 (1994).

94SL557 T. Itoh, H. Hasegawa, K. Nagata, and A. Ohsawa, *Synlett*, 557 (1994).

94T2405 P. Mátyus, K. Fuji, and K. Tanaka, *Tetrahedron* **50,** 2405 (1994).

94T12933 A. Katrusiak, A. Katrusiak, and S. Bałoniak, *Tetrahedron* **50,** 12933 (1994).

94T13089 T. Itoh, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *Tetrahedron* **50,** 13089 (1994).

94TL543 G. A. Crispino, A. Makita, Z.-M. Wang, and K. B. Sharpless, *Tetrahedron Lett.* **35,** 543 (1994).

94TL2709 J. Nakayama and K. Yoshimura, *Tetrahedron Lett.* **35,** 2709 (1994).

94TL2861 E. J. Corey, M. C. Noe, and S. Sarshar, *Tetrahedron Lett.* **35,** 2861 (1994).

94TL6559 B. B. Lohray, E. Nandanan, and V. Bhushan, *Tetrahedron Lett.* **35,** 6559 (1994).

94TL6745 R. N. Warrener, G. M. Elsey, I. V. Sankar, D. N. Butler, P. Pekos, and C. H. L. Kennard, *Tetrahedron Lett.* **35,** 6745 (1994).

94TL7685 K. J. Hale, V. M. Delisser, L.-K. Yeh, S. A. Peak, S. Manaviazar, and G. S. Bhatia, *Tetrahedron Lett.* **35,** 7685 (1994).

94ZOR1433 O. P. Krashykh, A. N. Maslivets, and Yu. S. Andreichikov, *Zh. Org. Khim.* **30,** 1433 (1994).

95ACS778 I. Mangalagiu, *Acta Chem. Scand.* **49,** 778 (1995).

95AF947 L. Castanier, C. Rubat, P. Coudert, E. Albuisson, J. Chopineau, and J. Couquelet, *Arzneim.-Forsch.* **45,** 947 (1995).

95AJC1267 M. Jalali-Heravi and M. Moosavi, *Aust. J. Chem.* **48,** 1267 (1995).

95AJC1549 A. A. Watson, D. A. House, and P. J. Steel, *Aust. J. Chem.* **48,** 1549 (1995).

95AJC1601 J. A. M. Guard and P. J. Steel, *Aust. J. Chem.* **48,** 1601 (1995).

95AP307 J. Easmon, G. Heinisch, W. Holzer, and B. Matuszczak, *Arch. Pharm. (Weinheim, Ger.)* **328,** 307 (1995).

95AP654 S. Corsano, G. Strappaghetti, R. Scapicchi, A. Lucacchini, and G. Senatore, *Arch. Pharm. (Weinheim, Ger.)* **328,** 654 (1995).

95AX(C)1834 S. Moreau, J. Metin, P. Coudert, and J. Couquelet, *Acta Crystallogr., Sect. C* **C51,** 1834 (1995).

95AX(D)496 V. L. Giranda, G. R. Russo, P. J. Felock, T. R. Bailey, T. Draper, D. J. Aldous, J. Guiles, F. J. Dutko, G. D. Diana, D. C. Pevear, and M. McMillan, *Acta Crystallogr., Sect. D* **D51,** 496 (1995).

95BMC3053 D. A. Nugiel, K. Jacobs, C. P. Decicco, D. J. Nelson, R. A. Copeland, and K. D. Hardman, *Bioorg. Med. Chem. Lett.* **5,** 3053 (1995).

95CP183 G. Fischer and P. Wormell, *Chem. Phys.* **198,** 183 (1995).

95CPB247 T. Seki, T. Takezaki, R. Ohuchi, H. Ohuyabu, Y. Tanimoto, T. Yamaguchi, M. Saitoh, T. Ishimori, and K. Yasuda, *Chem. Pharm. Bull.* **43,** 247 (1995).

95CPB535 Y. Arakawa, T. Gooto, K. Kawase, and S. Yoshifuji, *Chem. Pharm. Bull.* **43,** 535 (1995).

95H(40)1055 A. Godard, F. Marsais, N. Plé, F. Trécourt, A. Turck, and G. Quéguiner, *Heterocycles* **40,** 1055 (1995).

95H(41)1461 G. Heinisch, B. Matuszczak, K. Mereiter, and J. Soder, *Heterocycles* **41,** 1461 (1995).

95HAC281 Z. E. Kandeel, A. M. Farag, and F. M. Abdelrazek, *Heteroatom Chem.* **6,** 281 (1995).

95HAC469 S. Jolivet, T. Texier-Boullet, J. Hamelin, and P. Jacquault, *Heteroatom Chem.* **6,** 469 (1995).

95IJC(B)57 A. Y. Soliman, M. R. Mahmoud, and F. K. Mohamed, *Indian J. Chem., Sect. B* **34B,** 57 (1995).

95IJC(B)342 G. V. Subbaraju, K. S. Rao, G. S. Reddy, and Z. Urbanczyk-Lipkowska, *Indian J. Chem., Sect. B* **34B,** 342 (1995).

95JA10817 E. J. Corey, M. C. Noe, and A. Guzman-Perez, *J. Am. Chem. Soc.* **117,** 10817 (1995).

95JAN119 U. Gräfe, R. Schlegel, M. Ritzau, W. Ihn, K. Dornberger, C. Stengel,

W. F. Fleck, W. Gutsche, A. Härtl, and E. F. Paulus, *J. Antibiot.* **48,** 119 (1995).

95JCP4907 C. F. Dion and E. R. Bernstein, *J. Chem. Phys.* **103,** 4907 (1995).

95JCR(S)306 P. Powell and M. H. Sosabowski, *J. Chem. Res., Synop.*, 306 (1995).

95JCR(S)402 M. Sosabowski and P. Powell, *J. Chem. Res., Synop.*, 402 (1995).

95JCR(S)434 S. M. Sherif, R. M. Mohareb, H. Z. Shams, and H. M. M. Gaber, *J. Chem. Res., Synop.*, 434 (1995).

95JCS(CC)2067 T. Itoh, Y. Matsuya, K. Nagata, M. Okada, and A. Ohsawa, *J. Chem. Soc., Chem. Commun.*, 2067 (1995).

95JCS(CC)2201 R. Nesi, D. Giomi, S. Turchi, and A. Falai, *J. Chem. Soc., Chem. Commun.*, 2201 (1995).

95JCS(F1)1587 J. Jones, G. B. Bacskay, J. C. Mackie, and A. Doughty, *J. Chem. Soc., Faraday Trans 1* **91,** 1587 (1995).

95JCS(P1)2497 K. Matsumoto, M. Hashimoto, M. Toda, and H. Tsukube, *J. Chem. Soc., Perkin Trans 1*, 2497 (1995).

95JFC113 G. J. Chen and L. S. Chen, *J. Fluorine Chem.* **73,** 113 (1995).

95JHC13 G. Heinisch, B. Matuszczak, G. Pürstinger, and D. Rakowitz, *J. Heterocycl. Chem.* **32,** 13 (1995).

95JHC841 A. Turck, N. Plé, L. Mojovic, B. Ndzi, G. Quéguiner, N. Haider, H. Schuller, and G. Heinisch, *J. Heterocycl. Chem.* **32,** 841 (1995).

95JHC1057 F. Trécourt, A. Turck, N. Plé, A. Paris, and G. Quéguiner, *J. Heterocycl. Chem.* **32,** 1057 (1995).

95JHC1423 J. L. Kelley, J. B. Thompson, V. L. Styles, F. E. Soroko, and B. R. Cooper, *J. Heterocycl. Chem.* **32,** 1423 (1995).

95JHC1473 R. D. Bryant, F.-A. Kunng, and M. S. South, *J. Heterocycl. Chem.* **32,** 1473 (1995).

95JMC2925 N. J. S. Harmat, R. Giorgi, F. Bonaccorsi, G. Cerbai, S. M. Colombani, A. R. Renzetti, R. Cirillo, A. Subissi, F. Alagona, C. Ghio, F. Arcamone, A. Giachetti, F. Paleari, and A. Salimbeni, *J. Med. Chem.* **38,** 2925 (1995).

95JMC4878 D. W. Combs, K. Reese, and A. Phillips, *J. Med. Chem.* **38,** 4878 (1995).

95JMC4880 D. W. Combs, K. Reese, L. A. M. Cornelius, J. W. Gunnet, E. V. Cryan, K. S. Granger, J. J. Jordan, and K. T. Demarest, *J. Med. Chem.* **38,** 4880 (1995).

95JOC748 T. L. Draper and T. R. Bailey, *J. Org. Chem.* **60,** 748 (1995).

95JOC1466 M. Kočevar, P. Mihorko, and S. Polanc, *J. Org. Chem.* **60,** 1466 (1995).

95JOC3781 N. Plé, A. Turck, K. Couture, and G. Quéguiner, *J. Org. Chem.* **60,** 3781 (1995).

95JOC4919 A. Kotschy, G. Hajós, and A. Messmer, *J. Org. Chem.* **60,** 4919 (1995).

95JPR104 E. Fanghänel, A. Hucke, H. Hasan, K. Ullrich, R. Radeglia, and O. Simonsen, *J. Prakt. Chem.* **337,** 104 (1995).

95JPR347 E. Fanghänel, A. Hucke, and C. Zachert, *J. Prakt. Chem.* **337,** 347 (1995).

95JST(332)171 C. G. Mohan, A. Kumar, and P. C. Mishra, *J. Mol. Struct.* **332,** 171 (1995).

95JST(339)255 H. J. S. Machada and A. Hinchliffe, *J. Mol. Struct.* **339,** 255 (1995).

95JST(354)141 O. E. Kasende, F. M. Kabue, and M. Muzomwe, *J. Mol. Struct.* **354,** 141 (1995).

95LA169 G. Maier and F. Fleischer, *Liebigs Ann. Chem.* 169 (1995).
95LA173 G. Maier, F. Fleischer, and H.-O. Kalinowski, *Liebigs Ann. Chem.*, 173 (1995)
95M341 K. Gewald, H. Rehwald, H. Müller, P. Bellmann, and H. Schäfer, *Monatsh. Chem.* **126,** 341 (1995).
95M1265 E. Abdel-Ghani, M. G. Assy, and H. Y. Moustafa, *Monatsh.Chem.* **126,** 1265 (1995).
95MI1 M. Bruma, B. Schulz, and F. W. Mercer, *J. Macromol. Sci., Pure Appl. Chem.* **A32,** 259 (1995).
95MI2 F. W. Mercer, M. T. McKenzie, G. Merlino, and M. M. Fone, *J. Appl. Polym. Sci.* **56,** 1397 (1995).
95MI3 H. Tagawa, T. Tobita, H. Tomita, and T. Matsuzaki, *Biosci. Biotech. Biochem.* **59,** 1753 (1995).
95MI4 H. Sugimura, M. Motegi, and K. Sujino, *Nucleosides Nucleotides* **14,** 413 (1995).
95MI5 S. Corsano, R. Scapicchi, G. Strappaghetti, G. Marucci, and F. Paparelli, *Eur. J. Med. Chem.* **30,** 71 (1995).
95MI6 F. Billes and H. Mikosch, *J. Mol. Struct.* **349,** 409 (1995).
95PHA788 A. M. Hussein, A. A. Atalla, and A. M. K. El-Dean, *Pharmazie* **50,** 788 (1995).
95PJC685 M. G. Assy and E. A. El-Ghani, *Pol. J. Chem.* **69,** 685 (1995).
95PJC1642 A. M. Hussein, A. A. Atalla, and A. M. K. El-Dean, *Pol. J. Chem.* **69,** 1642 (1995).
95PS(101)189 A. A. Hassan, *Phosphorus Sulfur* **101,** 189 (1995).
95PS(102)51 S. E. Zayed, S. I. Aziz, A. W. Erian, R. M. Mohareb, E. I. A. Elmaged, S. A. Metwally, and M. H. Elnagdi, *Phosphorus Sulfur* **102,** 51 (1995).
95PS(106)167 A. A. Hassan, Y. R. Ibrahim, E.-S. H. El-Tamany, A. A. Semida, and A.-F. E. Mourad, *Phosphorus Sulfur* **106,** 167 (1995).
95S920 M. Guillaume, Z. Janousek, and H. G. Viehe, *Synthesis,* 920 (1995).
95S1240 F. Csende, Z. Szabó, G. Bernáth, and G. Stájer, *Synthesis*, 1240 (1995).
95SL615 C. P. Decicco and T. Leathers, *Synlett,* 615 (1995).
95T1585 S. A. Haroutounian and J. A. Katzenellenbogen, *Tetrahedron* **51,** 1585 (1995).
95T11855 G. Grassi, F. Risitano, and F. Foti, *Tetrahedron* **51,** 11855 (1995).
95T12745 H. Al-Awadhi, F. Al-Omran, M. H. Elnagdi, L. Infantes, C. Foces-Foces, N. Jagerovic, and J. Elguero, *Tetrahedron* **51,** 12745 (1995).
95TL5703 M. S. South and T. L. Jakuboski, *Tetrahedron Lett.* **36,** 5703 (1995).
95ZOB37 N. A. Polezhaeva, N. R. Fedotova, V. G. Sakhibullina, E. V. El'shina, and T.-G. Kostyunina, *Zh. Obshch. Khim.* **65,** 37 (1995).
96AF800 S. Moreau, P. Coudert, C. Rubat, E. Albuisson, and J. Couquelet, *Arzneim.-Forsch.* **46,** 800 (1996).
96AP433 K. A. Ismail, A. A. El-Tombary, O. M. A. Wafa, A. M. M. E. Omar, and S. H. El-Rewini, *Arch. Pharm. (Weinheim, Ger.)* **329,** 433 (1996).
96AX(C)1002 R. A. Jones, A. K. Powell, and A. P. Whitmore, *Acta Crystallogr., Sect. C* **C52,** 1002 (1996).
96AX(C)2622 A. J. Blake and H. McNab, *Acta Crystallgr., Sect. C* **C52,** 2622 (1996).

96BMC77 G. Holan, C. T. Virgona, K. G. Watson, and B. L. Finkelstein, *Bioorg. Med. Chem. Lett.* **6,** 77 (1996).

96CCC437 V. Konečný, and Š. Kováč, *Collect. Czech. Chem. Commun.* **61,** 437 (1996).

96CPB980 F. Rohet, C. Rubat, P. Coudert, E. Albuisson, and J. Couquelet, *Chem. Pharm. Bull.* **44,** 980 (1996).

96FA683 E. Gavini, C. Juliano, A. Mulè, G. Pirisino, G. A. Pinna, and M. M. Curzu, *Farmaco* **51,** 683 (1996).

96H151 G. Heinisch, W. Holzer, T. Langer, and P. Lukavsky, *Heterocycles* **43,** 151 (1996).

96H1057 G. Heinisch, T. Langer, J. Tonnel, K. Mereiter, and K. Wurst, *Heterocycles* **43,** 1057 (1996).

96H1459 M. Rohr, D. Toussaint, S. Chayer, A. Mann, J. Suffert, and C.-G. Wermuth, *Heterocycles* **43,** 1459 (1996).

96H1665 G. Heinisch, W. Holzer, K. Mereiter, B. Strobl, and C. Zheng, *Heterocycles* **43,** 1665 (1996).

96IJC(B)1097 M. S. Amine, M. A. Elhashash, F. M. A. Soliman, and A. S. Soliman, *Indian J. Chem., Sect. B* **35B,** 1097 (1996).

96JAN299 J. E. Leet, D. R. Schroeder, J. Golik, J. A. Matson, T. W. Doyle, K. S. Lam, S. E. Hill, M. S. Lee, J. L. Whitney, and B. S. Krishnan, *J. Antibiot.* **49,** 299 (1996).

96JAN811 T. Sato, Y. Takebayashi, T. Tokunaga, and T. Ozasa, *J. Antibiot.* **49,** 811 (1996).

96JCP2762 J. V. Ortiz and V. G. Zakrzewski, *J. Chem. Phys.* **105,** 2762 (1996).

96JCR(S)434 I. A. El-Sakka, *J. Chem. Res., Synop.,* 434 (1996).

96JCR(S)440 H. F. Zohdi, W. W. Wardakhan, S. H. Doss, and R. M. Mohareb, *J. Chem. Res., Synop.,* 440 (1996).

96JCR(S)448 G. A. McLean, B. J. L. Royles, D. M. Smith, and M. J. Bruce, *J. Chem. Res., Synop.,* 448 (1996).

96JCS(CC)2579 S. Brooker, R. J. Kelly, B. Moubaraki, and K. S. Murray, *J. Chem. Soc., Chem. Commun.,* 2579 (1996).

96JCS(D)2117 S. Brooker and R. J. Kelly, *J. Chem. Soc., Dalton Trans.,* 2117 (1996).

96JCS(P1)2517 R. Bernardi, B. Novo, and G. Resnati, *J. Chem. Soc., Perkin Trans. 1,* 2517 (1996).

96JHC213 R. Bakthavatchalam, E. Ciganek, and J. C. Calabrese, *J. Heterocycl. Chem.* **33,** 213 (1996).

96JHC245 S.-K. Kim, S.-D. Cho, D.-H. Kweon, S.-G. Lee, J.-W. Chung, S. C. Shin, and Y.-J. Yoon, *J. Heterocycl. Chem.* **33,** 245 (1996).

96JHC583 P. Mátyus, E. Zára-Kaczián, S. Boros, and Z. Böcskei, *J. Heterocycl. Chem.* **33,** 583 (1996).

96JHC615 S.-K. Kim, S.-D. Cho, J. K. Moon, and Y.-J. Yoon, *J. Heterocycl. Chem.* **33,** 615 (1996).

96JHC1579 S.-D. Cho, W.-Y. Choi, and Y.-J. Yoon, *J. Heterocycl. Chem.* **33,** 1579 (1996).

96JHC1731 G. Heinisch, T. Langer, and J. Tonnel, *J. Heterocycl. Chem.* **33,** 1731 (1996).

96JHC1915 D.-H. Kweon, S.-D. Cho, S.-K. Kim, J.-W. Chung, and Y.-J. Yoon, *J. Heterocycl. Chem.* **33,** 1915 (1996).

96JHC2059 B. Mernari and M. Lagrenée, *J. Heterocycl. Chem.* **33,** 2059 (1996).

96JMC297 Y. Nomoto, H. Tokai, T. Ohno, K. Nagashima, K. Yao, K. Yamada, K. Kubo, M. Ichimura, A. Mihara, and H. Kase, *J. Med. Chem.* **39,** 297 (1996).

96JMC4058 G. Heinisch, W. Holzer, F. Kunz, T. Langer, P. Lukavsky, C. Pechlaner, and H. Weissenberger, *J. Med. Chem.* **39,** 4058 (1996).

96JOC2001 J. W. Wijnen, S. Zavarise, J. B. F. N. Engberts, and M. Charton, *J. Org. Chem.* **61,** 2001 (1996).

96JOC4423 A. Kotschy, G. Hajós, G. Timári, and A. Messmer, *J. Org. Chem.* **61,** 4423 (1996).

96JOC6028 D. Gioni, R. Nesi, S. Turchi, and R. Coppini, *J. Org. Chem.* **61,** 6028 (1996).

96JOC8921 M. S. South, T. L. Jakuboski, M. D. Westmeyer, and D. R. Dukesherer, *J. Org. Chem.* **61,** 8921 (1966).

96JPC6973 J. M. L. Martin and C. Van Alsenoy, *J. Phys. Chem.* **100,** 6973 (1996).

96MI1 J. Easmon, G. Heinisch, and W. Holzer, *Sci. Pharm.* **64,** 37 (1996).

96MI2 A. A. Ahmed Boraei and O. M. El-Roudi, *Can. J. Appl. Spectrosc.* **41,** 37 (1996).

96MI3 J. I. Lee and S. H. Cho, *Bull. Korean Chem. Soc.* **17,** 868 (1996).

96MI4 V. Dal Piaz, M. P. Giovannoni, G. Ciciani, D. Barlocco, G. Giardina, G. Petrone, and G. D. Clarke, *Eur. J. Med. Chem.* **31,** 65 (1996).

96MI5 J. R. Greenwood, G. Vaccarella, H. R. Capper, K. N. Mewett, R. A. Allan, and G. A. R. Johnston, *J. Mol. Struct. (Theochem.)* **368,** 235 (1996).

96MRC728 R. A. Newmark, A. Tucker, and L. C. Hardy, *Magn. Reson. Chem.* **34,** 728 (1996).

96PHA76 J. Easmon, G. Heinisch, W. Holzer, and B. Matuszczak, *Pharmazie* **51,** 76 (1996).

96PHA528 K. Görlitzer and H. Berje, *Pharmazie* **51,** 528 (1996).

96RRC109 F. M. A. Soliman, M. A. El-Hashash, L. Souka, and A. S. Salman, *Rev. Roum. Chim.* **41,** 109 (1996).

96S223 U. Schmidt, C. Braun, and H. Sutoris, *Synthesis*, 223 (1996).

96S609 M. Kropf, H. Dürr, and C. Collect, *Synthesis*, 609 (1996).

96S838 N. Plé, A. Turck, K. Couture, and G. Quéguiner, *Synthesis*, 838 (1996).

96T1047 K. J. Hale, J. Cai, V. Delisser, S. Manaviazar, S. A. Peak, G. S. Bhatia, T. C. Collins, and N. Jogiya, *Tetrahedron* **52,** 1047 (1996).

96T5819 S. Jolivet, L. Toupet, F. Texier-Boullet, and J. Hamelin, *Tetrahedron* **52,** 5819 (1996).

96T6421 A. Corsaro, G. Perrini, V. Pistarà, P. Quadrelli, A. G. Invernizzi, and P. Caramella, *Tetrahedron* **52,** 6421 (1996).

96T8853 I. I. Mangalagiu, I. I. Druta, M. A. Constantinescu, I. V. Humelnicu, and M. C. Petrovanu, *Tetrahedron* **52,** 8853 (1996).

96T10417 L. Mojovic, A. Turck, N. Plé, M. Dorsy, B. Ndzi, and G. Quéguiner, *Tetrahedron* **52,** 10417 (1996).

96T13695 G. Baccolini, A. Munyaneza, and C. Boga, *Tetrahedron* **52,** 13695 (1996).

96T14975 D. Wensbo and S. Gronowitz, *Tetrahedron* **52,** 14975 (1996).

96TA2805 B. B. Lohray, E. Nandanan, and V. Bhushan, *Tetrahedron Asymmetry* **7,** 2805 (1996).

96TL1351 M. S. South, T. L. Jakuboski, M. D. Westmeyer, and D. R. Dukesherer, *Tetrahedron Lett.* **37,** 1351 (1996).

96TL4065 I. Gillies and C. W. Rees, *Tetrahedron Lett.* **37,** 4065 (1996).

96TL4145 L. Bourel, A. Tartar, and P. Melnyk, *Tetrahedron Lett.* **37,** 4145 (1996).

96TL5795 A. Rykowski and E. Woliñska, *Tetrahedron Lett.* **37,** 5795 (1996).

96TL8151 J. S. Panek and B. Zhu, *Tetrahedron Lett.* **37,** 8151 (1996).

96ZN(B)1334 H.-D. Stachel and J. Schachtner, *Z. Naturforsch., B* **51B,** 1334 (1996).

96ZOR591 V. N. Voshchula, A. N. Vdovichenko, A. V. Krivoruchko, and V. I. Dulenko, *Zh. Org. Khim.* **32,** 591 (1996).

97AP29 G. Heinisch, E. Huber, B. Matuszczak, A. Maurer, and U. Prillinger, *Arch. Pharm. Pharm. Med. (Weinheim. Ger.)* **330,** 29 (1997).

97BMC(5)655 F. Rohet, C. Rubat, P. Coudert, and J. Couquelet, *Bioorg. Med. Chem.* **5,** 655 (1997).

97BMC(7)275 D. Dorsch, W. W. K. R. Mederski, M. Osswald, R. M. Devant, C.-J. Schmitges, M. Christadler, and C. Wilm, *Bioorg. Med. Chem. Lett.* **7,** 275 (1997).

97CPB1151 R. Laguna, B. Rodriguez-Liñares, E. Cano, I. Estevez, E. Raviña, and E. Sotelo, *Chem. Pharm. Bull.* **45,** 1151 (1997).

97CPL272 H. Li, P. Dupre, and W. Kong, *Chem. Phys. Lett.* **273,** 272 (1997).

97FA67 E. Gavini, C. Juliano, A. Mule, G. Pirisino, and G. A. Pinna, *Farmaco* **52,** 67 (1997).

97FA173 V. Dal Piaz, G. Ciciani, and M. P. Giovannoni, *Farmaco* **52,** 173 (1997).

97H(45)2385 G. Heinisch, B. Matuszczak, and J. C. Wilke, *Heterocycles* **45,** 2385 (1997).

97H(46)83 T. Itoh, M. Miyazaki, K. Nagata, and A. Ohsawa, *Heterocycles* **46,** 83 (1997).

97JCR(S)236 A. A. Nada, A. W. Erian, N. R. Mohamed, and A. M. Mahran, *J. Chem. Res., Synop.*, 236 (1997).

97JCS(CC)2319 K. J. Hale and J. Cai, *J. Chem. Soc., Chem. Commun.*, 2319 (1997).

97JCS(P1)3485 M. S. F. L. K. Jie and P. Kalluri, *J. Chem. Soc., Perkin Trans. 1*, 3485 (1997).

97JCS(P2)857 C. A. Morrison, B. A. Smart, S. Parsons, E. M. Brown, D. W. H. Rankin, H. E. Robertson, and J. Miller, *J. Chem. Soc., Perkin Trans. 2*, 857 (1997).

97JHC389 J. Lange, J. Karolak-Wojciechowska, E. Pytlewska, J. Plenkiewicz, T. Kulinski, and S. Rump, *J. Heterocycl. Chem.* **34,** 389 (1997).

97JHC621 A. Turck, N. Plé, P. Pollet, L. Mojovic, J. Duflos, and G. Quéquiner, *J. Heterocycl. Chem.* **34,** 621 (1997).

97JHC1115 J. Svete, J. Golič, and B. Stanovnik, *J. Heterocycl. Chem.* **34,** 1115 (1997).

97JHC1135 S.-K. Kim, S.-D. Cho, and Y.-J. Yoon, *J. Heterocycl. Chem.* **34,** 1135 (1135).

97JHC1307 W.-Y. Choi, S.-D. Cho, S.-K. Kim, and Y.-J. Yoon, *J. Heterocycl. Chem.* **34,** 1307 (1997).

97JHC1421 G. Heinisch and B. Matuszczak, *J. Heterocycl. Chem.* **34,** 1421 (1997).

97JHC1629 S. Strah and B. Stanovnik, *J. Heterocycl. Chem.* **34,** 1629 (1997).

97JMC996 R. H. Bradbury, C. Bath, R. J. Butlin, M. Dennis, C. Heys, S. J. Hunt, R. James, A. A. Mortlock, N. F. Summer, E. K. Tang, B. Telford, E. Whiting, and C. Wilson, *J. Med. Chem.* **40,** 996 (1997).

97JMC4420 J. Easmon, G. Heinisch, G. Pürstinger, T. Langer, J. K. Österreicher, H. Grunicke, and J. Hofmann, *J. Med. Chem.* **40,** 4420 (1997).

97JOC5680 S. J. Miller and C. D. Bayne, *J. Org. Chem.* **62,** 5680 (1997).

97JOC7892 G. Ujaque, F. Maseras, and A. Lledós, *J. Org. Chem.* **62,** 7892 (1997).

97JPR623 T. Klindert, P. Hagel, L. Baumann, and G. Seitz, *J. Prakt. Chem.* **339,** 623 (1997).

97KGS1693 T. R. Akopyan and E. G. Paronikyan, *Khim. Geterotsikl. Soedin.,* 1693 (1997).

97MI1 B. C. Gerwick, S. S. Fields, P. R. Graupner, J. A. Gray, E. L. Chapin, J. A. Cleveland, and D. R. Heim, *Weed Sci.* **45,** 654 (1997).

97MI2 Z. G. Aliev, N. G. Vyaznikova, V. V. Zalesov, S. S. Kataev, Yu. S. Andreichikov, and L. O. Atovmyan, *Russ. Chem. Bull.* **46,** 2142 (1997) [*CA* **128,** 257406 (1998)].

97MI3 M. Bols, R. G. Hazell, and I. B. Thomsen, *Chem. Eur. J.* **3,** 940 (1997).

97MI4 S. Corsano, G. Strappaghetti, A. Leonardi, K. Rhazri, and R. Barbaro, *Eur. J. Med. Chem.* **32,** 339 (1997).

97MI5 D. M. Purohit and V. N. Shah, *Heterocycl. Commun.* **3,** 267 (1997).

97MI6 M. Takahashi and T. Yamaoka, *Heterocycl. Commun.* **3,** 521 (1997).

97MI7 J. R. Greenwood, H. R. Capper, R. D. Allan, and G. A. R. Johnston, *J. Mol. Struct.* **419,** 97 (1997).

97MI8 E. Mátrai, *J. Mol. Struct.* **408/409,** 467 (1997).

97PS133 A. W. Erian, Y. M. Elkholy, E. Ezz Al-Arab, and M. H. Elnagdi, *Phosphorus Sulfur* **122,** 133 (1997).

97S91 F. Al-Omran, M. M. A. Khalik, A. Abou-Elkhair, and M. H. Elnagdi, *Synthesis,* 91 (1997).

97S1495 M. Msaddek, M. Rammah, K. Ciamala, J. Vebrel, and B. Laude, *Synthesis,* 1495 (1997).

97SC2419 E. Sotelo, R. Mocelo, M. Suárez, and A. Loupy, *Synth. Commun.* **27,** 2419 (1997).

97SL1361 O. A. Attanasi, P. Filippone, C. Fiorucci, and F. Mantellini, *Synlett,* 1361 (1997).

97T3707 G. Verardo, N. Toniutti, and A. G. Giumanini, *Tetrahedron* **53,** 3707 (1997).

97T4411 I. I. Mangalagiu and M. G. Petrovanu, *Tetrahedron* **53,** 4411 (1997).

97T9357 I. Thomsen, B. V. Ernholt, and M. Bols, *Tetrahedron* **53,** 9357 (1997).

97T10591 M. Tiecco, L. Testaferri, F. Marini, C. Santi, L. Bagnoli, and A. Temperini, *Tetrahedron* **53,** 10591 (1997).

97T11711 S. Turchi, D. Giomi, C. Capaccioli, and R. Nesi, *Tetrahedron* **53,** 11711 (1997).

97TL3805 S. M. Sakya, K. K. Groskopf, and D. L. Boger, *Tetrahedron Lett.* **38,** 3805 (1997).

97TL5791 D. K. Heldman and J. Sauer, *Tetrahedron Lett.* **38,** 5791 (1997).

97TL5913 S. M. Sakya, T. W. Strohmeyer, S. A. Lang, and Y.-I. Lin, *Tetrahedron Lett.* **38,** 5913 (1997).

97TL8611 K. Daly, R. Nomak, and J. K. Snyder, *Tetrahedron Lett.* **38,** 8611 (1997).

97ZOB1651 N. I. Tyryshkin, N. A. Polezhaeva, V. G. Sakhibullina, and G. A. Chmutova, *Zh. Obshch. Khim.* **67,** 1651 (1997).

98AG(E)2993 T. M. Kamenecka and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.* **37,** 2993 (1998).

98AG(E)2995 T. M. Kamenecka and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.* **37,** 2995 (1998).

98H2221 Y. Kamitori, M. Hojo, and T. Yoshioka, *Heterocycles* **48,** 2221 (1998).

98HCA231 L. Pizzioli, B. Ornik, J. Svete, and B. Stanovnik, *Helv. Chim. Acta* **81,** 231 (1998).

98JCS(P1)1637 T. Itoh, Y. Matsuya, K. Nagata, M. Miyazaki, N. Tsutsumi, and A. Ohsawa, *J. Chem. Soc., Perkin Trans. 1*, 1637 (1998).

98JCS(P2)269 N. R. Hore and D. K. Russell, *J. Chem. Soc., Perkin Trans. 2*, 269 (1998).

98JHC429 A. Turck, N. Plé, P. Pollet, and G. Quéguiner, *J. Heterocycl. Chem.* **35,** 429 (1998).

98JHC595 Y.-J. Kang, H.-A. Chung, D.-H. Kweon, S.-D. Cho, S.-G. Lee, S.-K. Kim, and Y.-J. Yoon, *J. Heterocycl. Chem.* **35,** 595 (1998).

98JHC601 S.-D. Cho, D.-H. Kweon, Y.-J. Kang, H.-A. Chung, and Y.-J. Yoon, *J. Heterocycl. Chem.* **35,** 601 (1998).

98JHC819 D.-H. Kweon, Y.-J. Kang, H.-A. Chung, and Y.-J. Yoon, *J. Heterocycl. Chem.* **35,** 819 (1998).

98JMC311 Y. Rival, R. Hoffmann, B. Didier, V. Rybaltchenko, J.-J. Bourguignon, and C. G. Wermuth, *J. Med. Chem.* **41,** 311 (1998).

98JOC4912 J. Nakayama, R. Hasemi, K. Yoshimura, Y. Sugihara, S. Yamaoka, and N. Nakamura, *J. Org. Chem.* **63,** 4912 (1998).

98JOC9880 O. A. Attanasi, P. Filippone, C. Fiorucci, E. Foresti, and F. Mantellini, *J. Org. Chem.* **63,** 9880 (1998).

98MI1 J. Sauer, D. K. Heldmann, J. Hetzenegger, J. Krauthan, H. Sichert, and J. Schuster, *Eur. J. Org. Chem.* 2885 (1998).

98MI2 C. Olier-Reuchet, D. J. Aitken, and H.-P. Husson, *Heterocycl. Commun.* **4,** 59 (1998).

98MI3 F. Billes, H. Mikosch, and S. Holly, *J. Mol. Struct.* **423,** 225 (1998).

98S1627 A. R. Katritzky, D. P. M. Pleynet, B. Yang, and J. Yao, *Synthesis,* 1627 (1998).

98SL762 V. Dal Piaz and A. Capperucci, *Synlett,* 762 (1998).

98SL1279 O. Poupardin, C. Greck, and J.-P. Genêt, *Synlett,* 1279 (1998).

98T1809 S. Turchi, R. Nesi, and D. Giomi, *Tetrahedron* **54,** 1809 (1988).

98T4297 J. Sauer and D. K. Heldmann, *Tetrahedron* **54,** 4297 (1998).

98T6553 R. S. Reddy, K. Saravanan, and P. Kumar, *Tetrahedron* **54,** 6553 (1998).

98T9519 R. A. Jones and A. P. Whitmore, *Tetrahedron* **54,** 9519 (1998).

98T10851 R. Nesi, S. Turchi, D. Giomi, and C. Corsi, *Tetrahedron* **54,** 10851 (1998).

98T12897 A. R. Al Dulayymiand M. S. Baird, *Tetrahedron* **54,** 12897 (1998).

98TL841 S. Chayer, E. M. Essassi, and J.-J. Bourguignon, *Tetrahedron Lett.*, 841 (1998).

98TL5873 T. J. Sparey and T. Harrison, *Tetrahedron Lett.* **39,** 5873 (1998).

ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 75

The Chemistry of 1,2,4-Triazolopyrimidines II: 1,2,4-Triazolo[4,3-*c*]Pyrimidines

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I. Introduction

This is the second part of the review on the chemistry of 1,2,4-triazolopyrimidines. The first part [99AHC(73)131] was devoted to surveying the chemistry of one of the four possible systems of this class of compounds, namely 1,2,4-triazolo[4,3-*a*]pyrimidines. The third and last part should comprise the chemistry of 1,2,4-triazolo[1,5-*c*]pyrimidines and will be published in a forthcoming volume of this series. G. Fischer has recently reviewed the chemistry of the fourth system, 1,2,4-triazolo[1,5-*a*]pyrimidines [93AHC(57)81].

To coincide with the organization of the first part [99AHC(73)131], this chapter is also classified into five major sections: Introduction, Synthesis, Reactions, Spectral properties, and Applications. The literature has been searched to issue number 10 volume 129, 1998 of *Chemical Abstracts*.

II. Synthesis

Many members of the 1,2,4-triazolo[4,3-*c*]pyrimidines were shown to possess very interesting biological activities and medicinal applications (Section V). Yet, the body of published work on the synthesis of these compounds revealed that it is the least studied of the four 1,2,4-triazolopyrimidine systems. This is due, most probably, to their facile transformation under most of the utilized conditions of synthesis to the corresponding thermodynamically more stable 1,2,4-triazolo[1,5-*c*]pyrimidine regioisomers (Dimroth-like rearrangement). 1,2,4-Triazolo[4,3-*c*]pyrimidines have been synthesized using the following general approaches: (1) annulation of the 1,2,4-triazole ring onto a pyrimidine structure; (2) annulation of the pyrimidine ring onto a 1,2,4-triazole structure; (3) concurrent formation of both of the 1,2,4-triazole and pyrimidine rings, and (4) rearrangement of pyrimido[5,4-*e*]1,2,4-triazines.

A. Synthesis by Annulation of the 1,2,4-Triazole Ring onto a Pyrimidine Structure

This approach has been implemented by cyclization of suitable pyrimidine derivatives as explained in the following schematic presentations:

(1) Two-bond formation through (4 + 1) heterocyclization of pyrimidine derivatives bearing two nitrogen atoms at C4 or C6 [4(6)-hydrazinopyrimidines] by reaction with one-carbon cyclizing reagents (aldehydes, acids, or acid derivatives) (Scheme 1).

(2) Two-bond formation through (2 + 3) heterocyclization of pyrimidine derivatives carrying a good leaving group at C4 or C6 [e.g., 4(6)-halo- or mercaptopyrimidines] with reagents containing one carbon and two adjacent nitrogen atoms (e.g., arylidenehydrazines and acylhydrazines) (Scheme 2).

(3) Two-bond formation through (3 + 2) heterocyclization of pyrimidine derivatives carrying one nitrogen at C4 or C6 [4(6)-aminopyrimidines] by reaction with reagents containing one carbon and one nitrogen atoms (e.g., imidate esters) (Scheme 3).

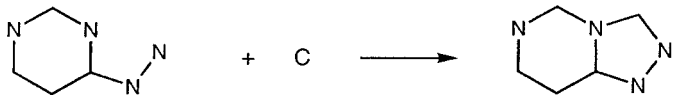
(4) One-bond formation by thermolytic cyclization of 4-(tetrazol-2-yl)pyrimidines (Scheme 4).

1. *Cyclization of 4(6)-Hydrazinopyrimidines by Reaction with One-Carbon Cyclizing Reagents*

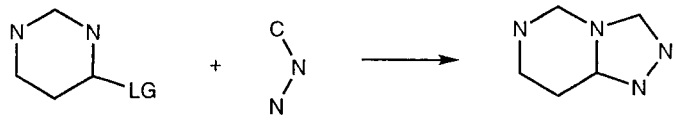
Condensation of 4(6)-hydrazinopyrimidines (**1**) with aryl or heterocyclic aldehydes gave the corresponding 4(6)-arylidenehydrazinopyrimidines **2.** Oxidative cyclization of **2** with lead tetraacetate (57JCS727; 71GEP-2004713) or with ethanolic iron (III) chloride [94JCR(S)412] afforded the respective 3-substituted 1,2,4-triazolo[4,3-*c*]pyrimidines **3** (Scheme 5).

Nitrozation of 6-benzylidenehydrazino-3-methyluracil **4** took place with concurrent cyclization to **5.** The latter was also obtained from the nitroso and the nitro derivatives **6** and **7** upon treatment with a mixture of sodium or potassium nitrate and acetic and sulfuric acids (75CPB1885) (Scheme 6).

Aldehyde acetals have also been utilized to accomplish cyclization of 4(6)-hydrazinopyrimidines such as **8** to **9** (76S833; 81USP4269980) (Scheme 7).

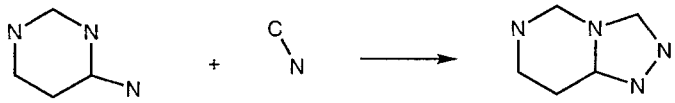


Scheme 1

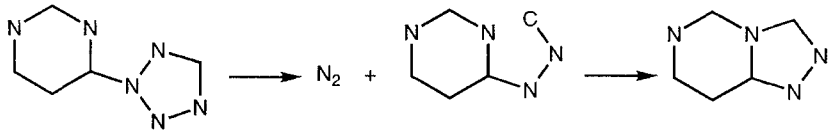


LG = leaving group

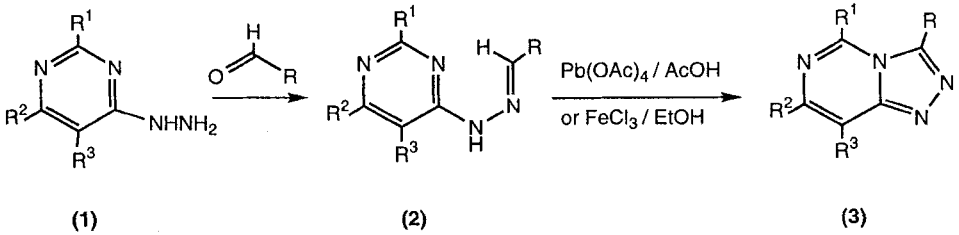
SCHEME 2



SCHEME 3

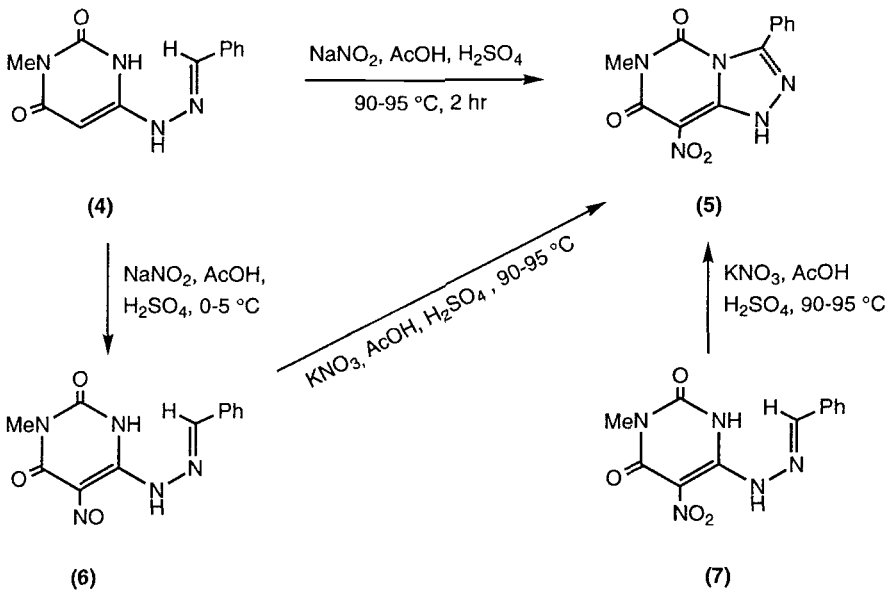


SCHEME 4



R = 4-C_6H_4Y, O_2N-(furan-2-yl); R^1 = H, Me, SMe, NHPh; R^2 = Me, NH_2; R^3 = H, Me

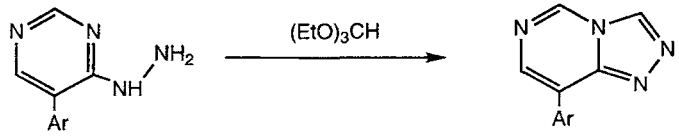
SCHEME 5



SCHEME 6

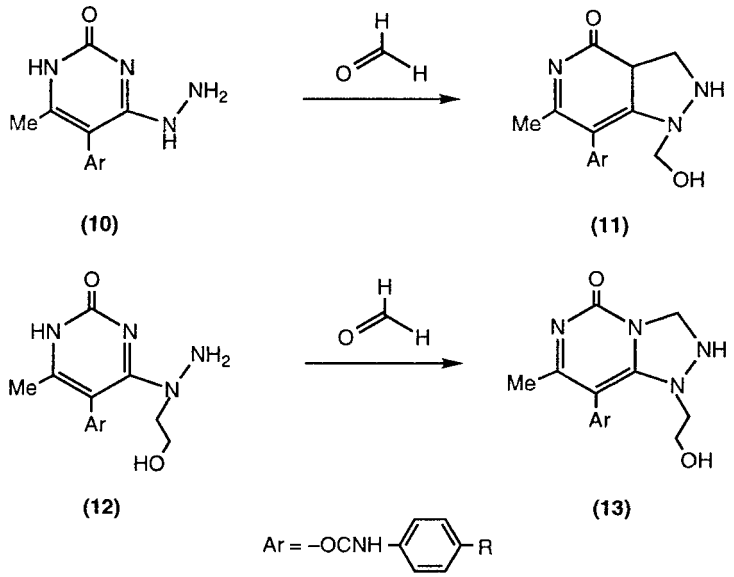
1-Substituted-2,3-dihydro-1,2,4-triazolo[4,3-*c*]pyrimidines **11** and **13** were obtained as a result of cyclocondensation and simultaneous hydroxymethylation of **10** (89AP599) and cyclocondensation of **12** with formaldehyde (92PJC131) (Scheme 8).

1,2,4-Triazolo[4,3-*c*]pyrimidines **16** were prepared by cyclization of 4-hydrazinopyrimidines carrying various substituents (**14**) with carboxylic acids. Whereas cyclization with formic acid afforded the 3-unsubstituted **16** (R=H) (60G1821, 60G1830; 66JOC900; 75JHC551; 89MI1; 91AKZ448, 91MI1; 93EUP521768), cyclization with other carboxylic acids gave the 3-substituted **16** (R=alkyl or aryl) (56JPJ804; 60GEP1074589; 80AJC1147;



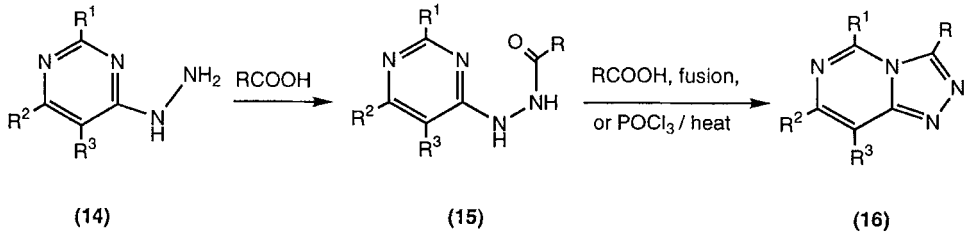
Ar = 4-ClC$_6$H$_4$

SCHEME 7



SCHEME 8

89MI1). This cyclization was also performed with acid chlorides (60GEP1074589; 66MI1; 70CB3278) as well as acid anhydrides (56JPJ804; 60GEP1074589; 66MI1; 71MI1; 78PJC37; 89PHA604; 98TL3865). Occasionally, it was possible to isolate the acylhydrazinopyrimidine intermediates **15** (56JPJ804; 60GEP1074589; 66JOC900, 66MI1; 70CB3278; 90T3897; 98TL3865), which were dehydrocyclized in a separate step to **16** by further heating with the same carboxylic acid (56JPJ804; 66JOC900), a mineral acid (98TL3865), by fusion (60GEP1074589), or by heating with phosphoryl chloride (70CB3278; 90T3897) (Scheme 9).

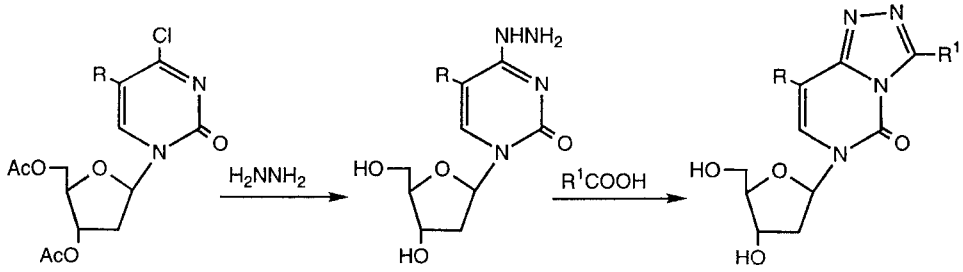


SCHEME 9

Contradictory results have sometimes been encountered regarding the assignment of structures of compounds prepared according to this method due to the ease of rearrangement of 1,2,4-triazolo[4,3-*c*]pyrimidines to 1,2,4-triazolo[1,5-*c*]pyrimidines under the acidic reaction conditions (Dimroth rearrangement, Section III,A). Thus, whereas La Noce and Giuliani (75JHC551) explicitly stated that such a rearrangement did not take place, Brown *et al.* (79AJC1585; 80AJC1147) showed, on the basis of ^{1}H-NMR studies, that it did take place. An interesting result reported the synthesis of the 6-(2-deoxy-β-D-ribofuranosyl)-1,2,4-triazolo-[4,3-*c*]pyrimidin-5-one nucleosides **19** by cyclization of the corresponding hydrazinopyrimidine nucleosides **18** with formic or acetic acids; neither the sugar–heterocycle bond hydrolysis of **18** or **19** nor a Dimroth rearrangement of **19** were observed under the acidic reaction conditions (89MI1; 91MI1) (Scheme 10).

Carboxylic acid esters (89PHA604; 90T3897; 93KGS1545), dithioesters [89H(28)239], imidic acid esters, and thioesters (89JHC991) were also utilized as one-carbon cyclizing agents to bring about heterocyclization of 4-hydrazinopyrimidines to 1,2,4-triazolo[4,3-*c*]pyrimidines.

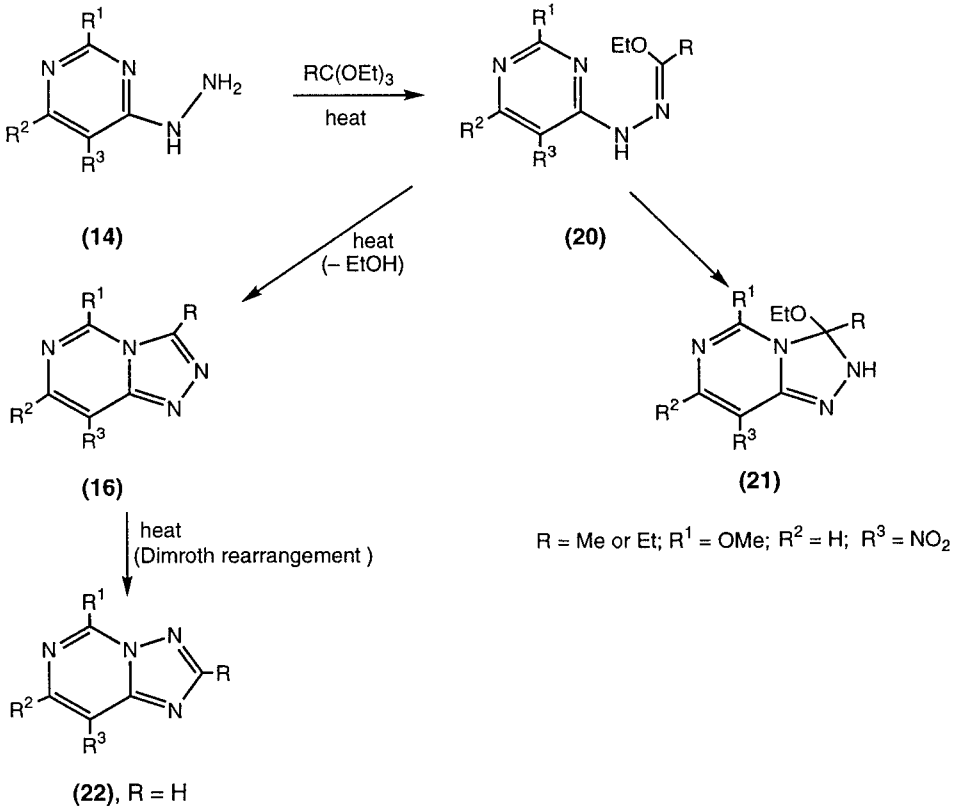
Reaction of **14** with acid orthoesters gave **16** through cyclocondensation of the occasionally isolable 1-ethoxyalkylidene-2-(pyrimidin-4-yl)-hydrazine intermediates **20** [70JCS(C)139; 71AJC633; 72JCS(P1)2316; 75JHC551; 76S833; 78AJC2505; 79AJC1585; 80AJC1147; 84EUP121341; 85USP4532242; 86TL3127, 86USP4591588; 89JHC687; 90H(31)277; 92KGS225; 94JMC2371]. In one case, however, the formation of the 3-alkyl-3-ethoxy-2,3-dihydro-1,2,4-triazolo[4,3-*c*]pyrimidine **21** as a result of intramolecular additive cyclization of the corresponding **20** was reported [72JCS(P1)2316] (Scheme 11).



(17) **(18)** **(19)**

R = H or Me; R^1 = H or Me

SCHEME 10



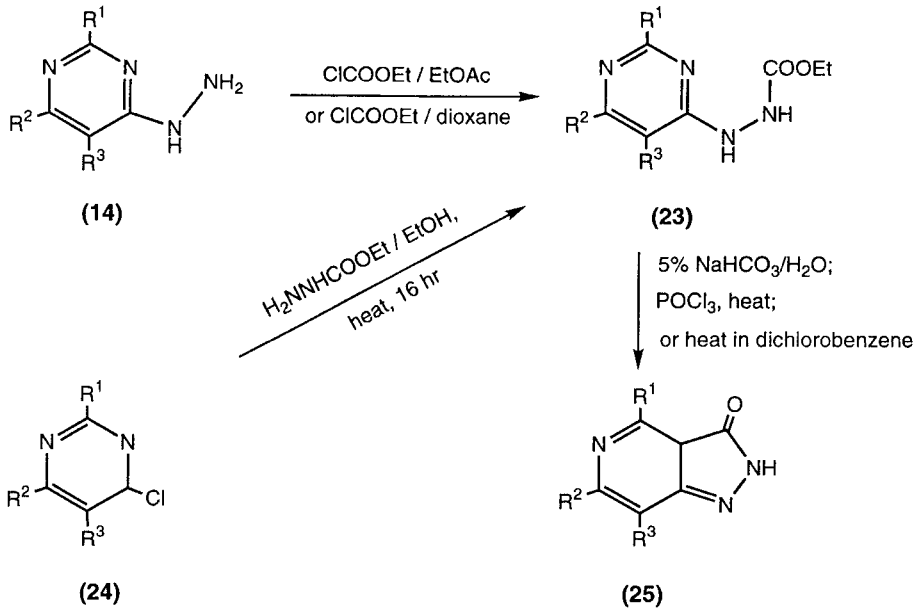
SCHEME 11

The 2-unsubstituted 1,2,4-triazolo[1,5-*c*]pyrimidines **22** (R=H) were sometimes formed as a result of Dimroth rearrangement of the transient **16** (R=H) [76S833; 80AJC1147; 89JHC687; 90H(31)277] (Scheme 11).

3-Oxo-1,2,4-triazolo[4,3-*c*]pyrimidines (**25**) were prepared by cyclization of the 4-(2-ethoxycarbonylhydrazino)pyrimidines **23** by heating with an aqueous solution of sodium hydrogen carbonate (63JOC2257) or phosphoryl chloride (65JCS3357) or by heating in dichlorobenzene (65JCS3357). Compounds **23** were synthesized from 4-hydrazinopyrimidines (**14**) and ethyl chloroformate (63JOC2257; 65JCS3357) or from 2-chloropyrimidines (**24**) and ethoxycarbonylhydrazine (65JCS3357) (Scheme 12).

Cyclocarbonylation of 4-hydrazinopyrimidines (**14**) with phosgene also gave **25** (65JCS3357; 68JOC530; 85USP4528288), which may rearrange under reaction conditions to the regioisomeric 3-oxo-1,2,4-triazolo[1,5-*c*]-pyrimidines **26** (85USP4528288) (Scheme 13).

Cyclocarbonylation of **14** has also been made with 1,1′-carbonyldiimidazole (94JMC2371) or by heating with urea in the presence of *N*-methylpyrrolidine

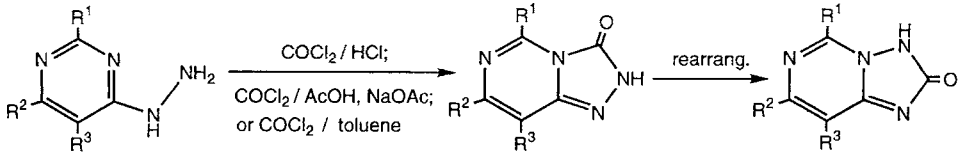


SCHEME 12

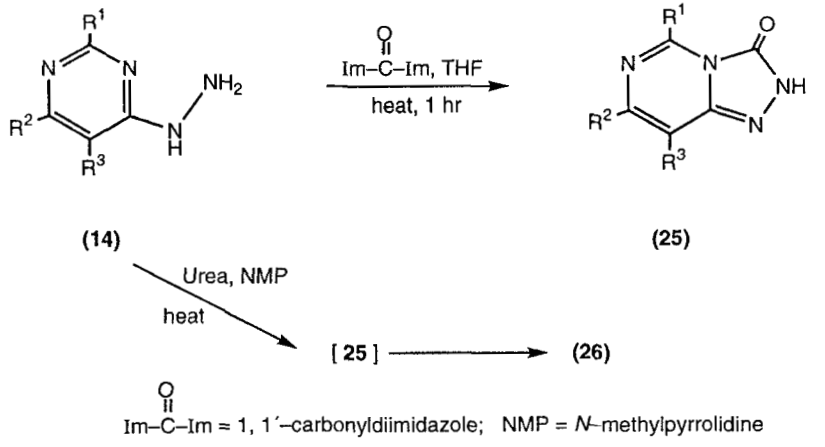
(96JHC1307). Whereas the former cyclization afforded **25,** the latter gave **26** as a result of Dimroth rearrangement of the initially formed **25** (Scheme 14).

Reaction of carbon disulfide with 4-hydrazinopyrimidine (**14**) afforded the 3-thioxo-1,2,4-triazolo[4,3-*c*]pyrimidines **28.** The reaction has usually been carried out in an alcohol in the absence (64BRP951652; 94JMC2371; 95MIP2) or in the presence of triethylamine (65JCS3369; 75JHC551; 95MIP3), potassium or sodium hydroxide [66MI1; 79AJC2713; 89JHC313; 94JCR(S)412], or sodium ethoxide (89EUP343752; 95MIP1). Compounds **28** are usually the end-products of this reaction, yet rearrangement to the regioisomeric 2-thioxo-1,2,4-triazolo[1,5-*c*]pyrimidines **29** has sometimes been reported (64BRP951652; 89EUP343752; 94JMC2371) (Scheme 15).

Cyclization of **14** with cyanogen chloride or cyanogen bromide in aqueous ethanol in the presence of sodium carbonate or sodium acetate is the



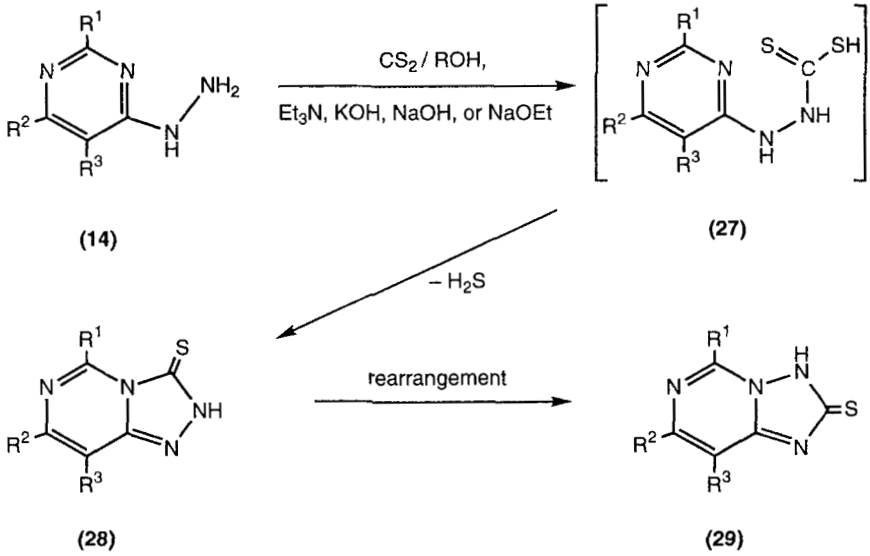
SCHEME 13



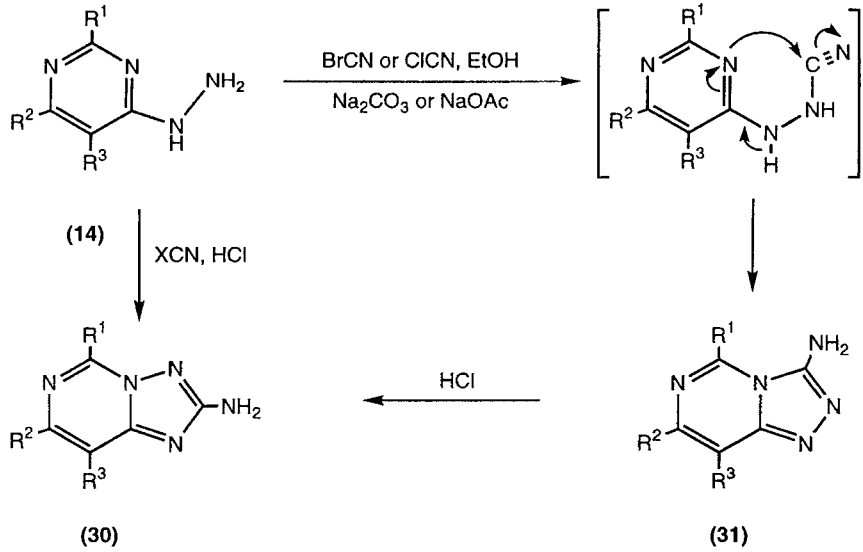
SCHEME 14

method of choice for the preparation of the 3-amino-1,2,4-triazolo[4,3-*c*]pyrimidines **31** (61BRP859287; 62BRP898408; 63JCS5642). Carrying out this cyclization in aqueous hydrochloric acid usually affords the 2-amino-1,2,4-triazolo[1,5-*c*]pyrimidines **30** presumably through the intermediacy of the respective **31** (85GEP3427823; 90JMC1230) (Scheme 16).

Condensation of **14** with methyl isocyanate gave the 1-(pyrimidin-4-yl)-4-methylsemicarbazides **32** which cyclodehydrated to the 3-methylamino-



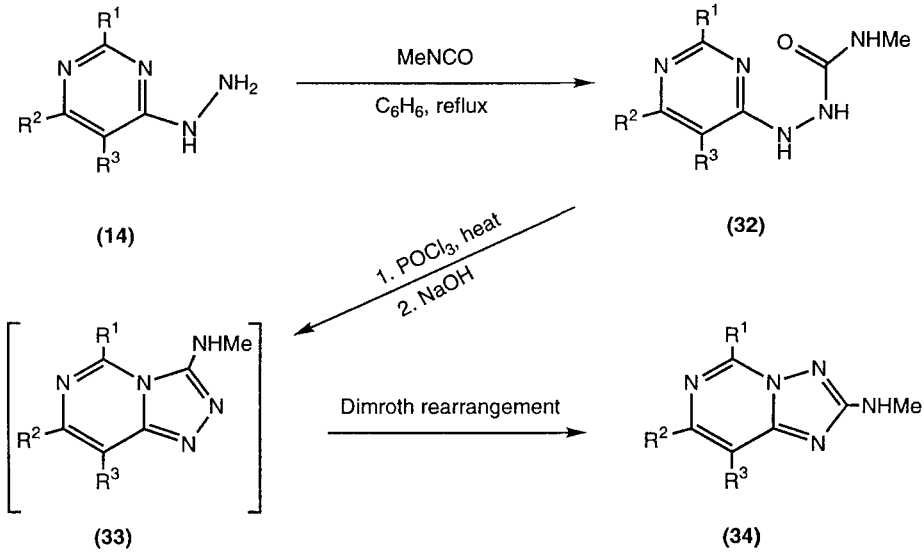
SCHEME 15



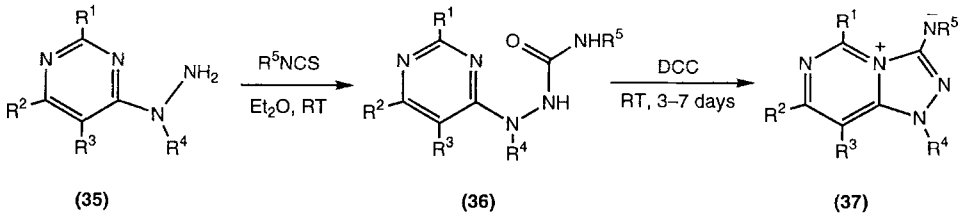
SCHEME 16

1,2,4-triazolo[4,3-*c*]pyrimidines **33** that isomerized to the [1,5-*c*] regioisomers **34** (62BRP897870) (Scheme 17).

The mesoionic 1-alkyl-3-alkylamino-1,2,4-triazolo[4,3-*c*]pyrimidines **37** were obtained by cyclization of the 1,4-dialkyl-1-(pyrimidin-4-yl)thio-



SCHEME 17



(35) (36) (37)

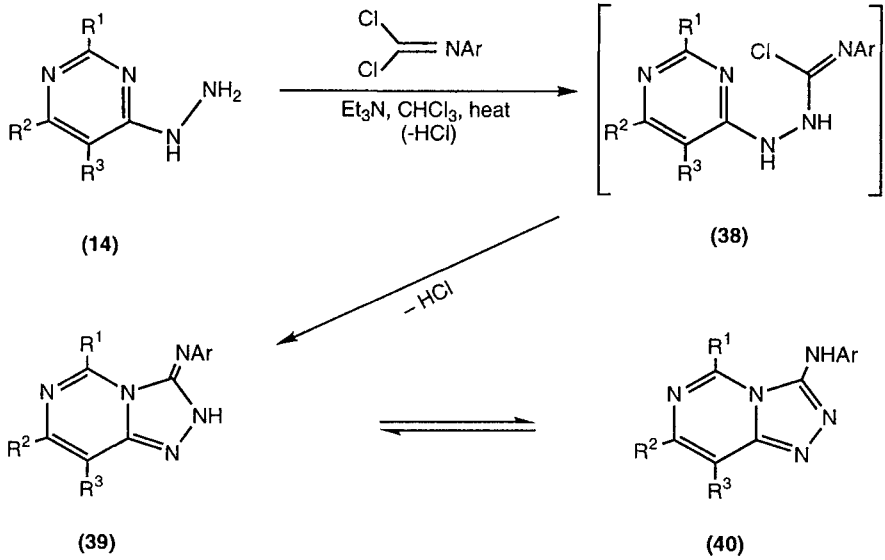
SCHEME 18

semicarbazides **36** with dicyclohexylcarbodiimide (DCC) [97JCS(P2)49] (Scheme 18).

The 3-arylamino-1,2,4-triazolo[4,3-*c*]pyrimidines **40** were regiospecifically formed upon cyclization of **14** with *N*-aryl phosgenimines (aryl isocyanide dichlorides). Rearrangement to the respective [1,5-*c*] isomers did not occur and the structure (**40**) was corroborated by X-ray diffraction analysis (90T3897) (Scheme 19).

2. *Cyclization of Pyrimidines Carrying a Good Leaving Group at C4 or C6 by Reaction with Reagents Containing One Carbon and Two Adjacent Nitrogen Atoms*

Cyclocondensation of the 2-amino-5-alkyl-4-chloro-5-phenylpyrimidines **41** with formylhydrazine gave the corresponding 1,2,4-triazolo[4,3-*c*]pyrim-



(14) (38) (39) (40)

SCHEME 19

idines **43** (81GEP3029871) or a mixture of **43** and their [1,5-*c*] regioisomers **44** (83USP4405780) (Scheme 20).

Reaction of cytidine (**45a**) or 2′-deoxycytidine (**45b**) with diformylhydrazine (**46**) in the presence of trimethylsilyl chloride as a Lewis acid gave the 6-glycosyl-1,2,4-triazolo[4,3-*c*]pyrimidin-5-ones **50.** The 1,2,4-triazolyl moiety of the initially formed 4-(1,2,4-triazol-4-yl)pyrimidine derivatives **47** underwent displacement with diformylhydrazine to give the 4-(1,2-diformylhydrazino)pyrimidines **49,** which then cyclized to **50** (Scheme 21) (95JOC7066).

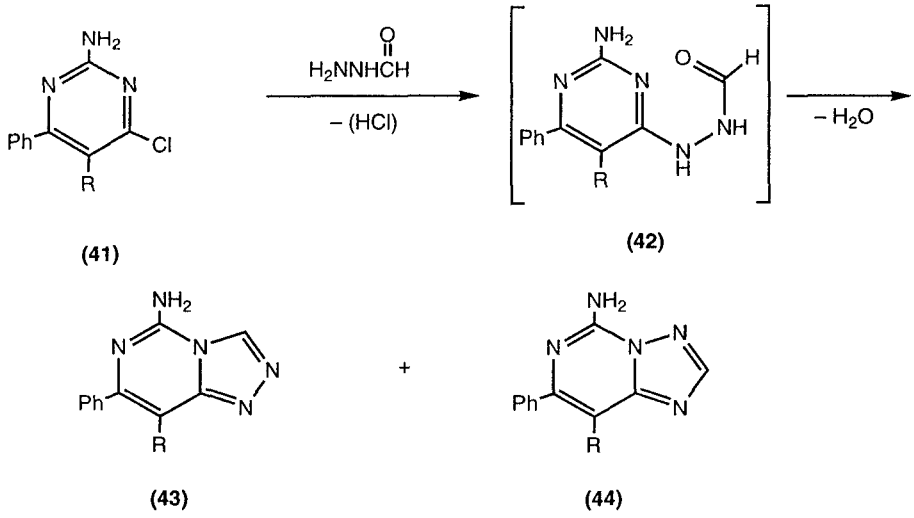
The preparation of the previously mentioned 3-oxo-1,2,4-triazolo[4,3-*c*]pyrimidine (**25**) from 4-chloropyrimidines (**24**) and ethoxycarbonylhydrazine (65JCS3357) (see Scheme 12) also belongs to this approach.

3. *Cyclization of 4(6)-Aminopyrimidines by Reaction with Reagents Containing One Carbon and One Nitrogen Atom*

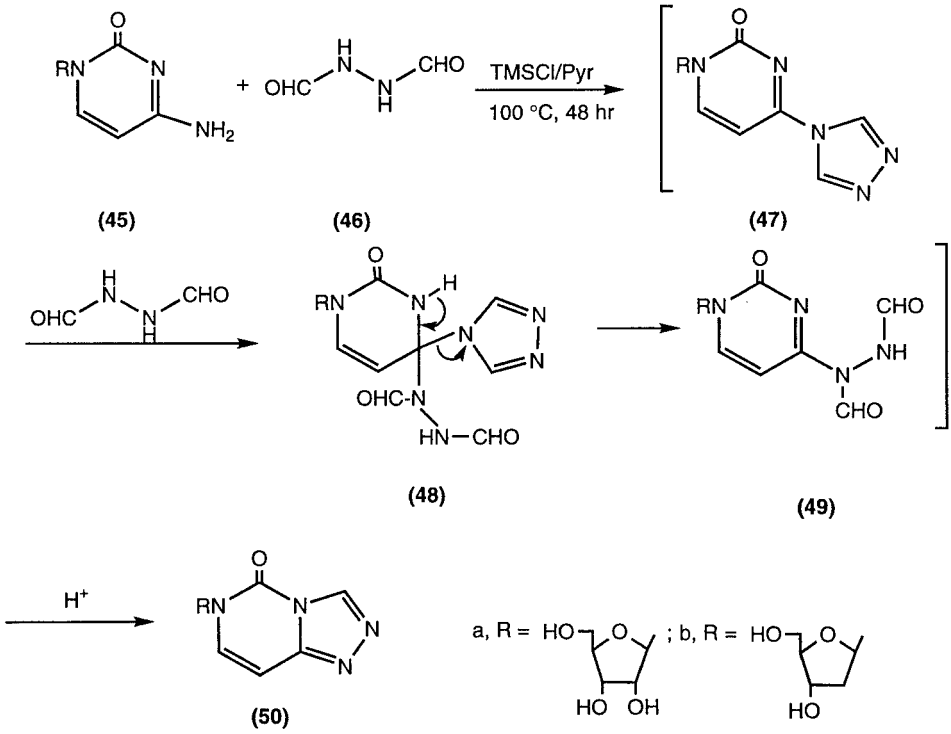
Cyclization of cytidine (**45a**), cytosine (**45c**), or cytidine-5-phosphate (**45d**), with ethyl acetimidate gave the respective 5,6-dihydro-3-methyl-1,2,4-triazolo[4,3-*c*]pyrimidine-5-ones **51** (78MI1) (Scheme 22).

4. *Thermolytic Cyclization of 4-(Tetrazol-2-yl)pyrimidines*

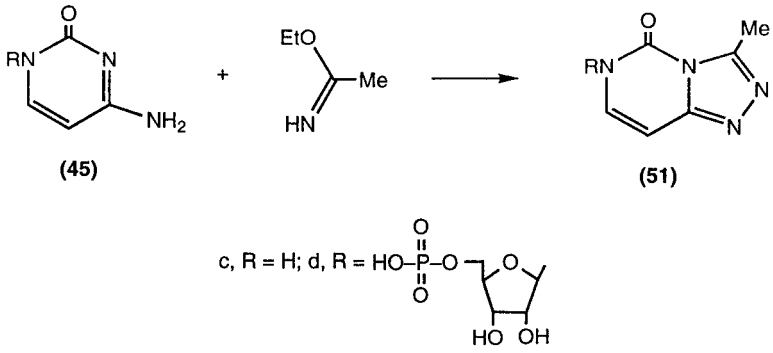
Thermolysis of 4-(5-phenyltetrazol-2-yl)pyrimidines (**53**), obtained from 4-chloropyrimidines (**24**) and 5-phenyltetrazole (**52**), gave the corresponding 2-phenyl-1,2,4-triazolo[4,3-*c*]pyrimidines **55** as a result of cyclization of



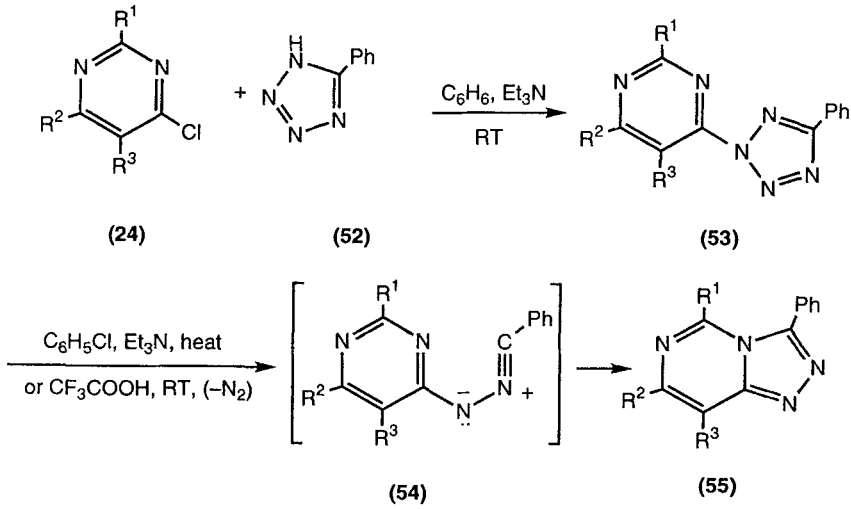
SCHEME 20



SCHEME 21



SCHEME 22



(24) (52) (53) (54) (55)

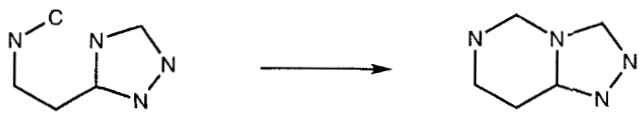
SCHEME 23

the nitrilimine intermediates **54** (77TL2187; 78TL2071) (Scheme 23). This route amounts to cyclization of 4-chloropyrimidines (**24**) with benzoylhydrazine.

B. Synthesis by Annulation of the Pyrimidine Ring onto a 1,2,4-Triazole Structure

1,2,4-Triazolo[4,3-*a*]pyrimidines have frequently been synthesized by this approach, which involves the facile cyclization of 3-amino-1,2,4-triazoles with three-carbon cyclizing fragments through two-bond formation. In the case of 1,2,4-triazolo[4,3-*c*]pyrimidines, however, the comparable synthetic approach has been studied only meagerly. So far, only two reaction pathways were utilized: (1) Two-bond formation through (5 + 1) heterocyclization of 1,2,4-triazoles carrying an appendage of two carbons and one nitrogen at C3 by reaction with one-carbon cyclizing reagents (Scheme 24) and (2) One-bond formation by intramolecular cyclization of 1,2,4-triazoles having a -C-C-N-C- appendage at C3 (Scheme 25).

SCHEME 24



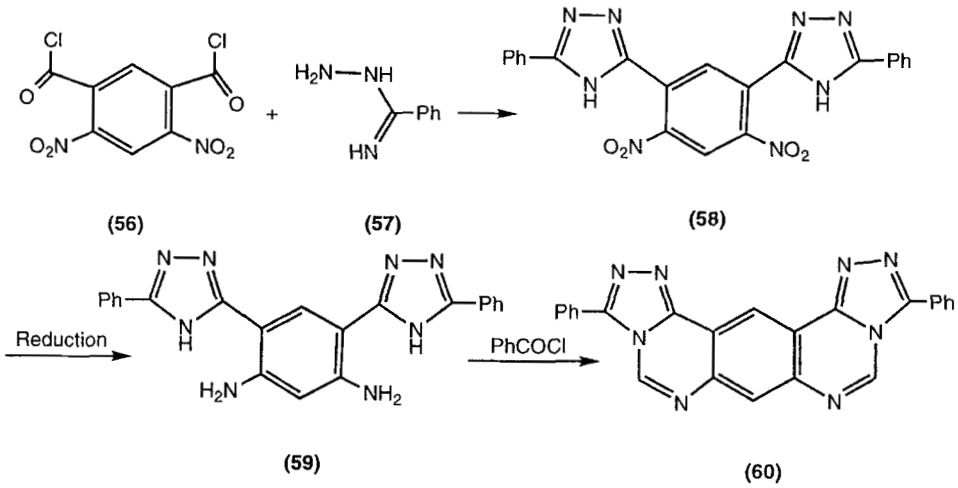
SCHEME 25

1. *Cyclization of 3-(2-Aminophenyl)-1,2,4-triazoles by Reaction with One-Carbon Cyclizing Reagents*

The pentacyclic benzo-bis{1,2,4-triazolo[4,3-*c*]pyrimidine} **60** was prepared from 4,6-dinitroisophthaloyl dichloride (**56**) and benzimidrazone (**57**) as shown in scheme 26 (76MI1).

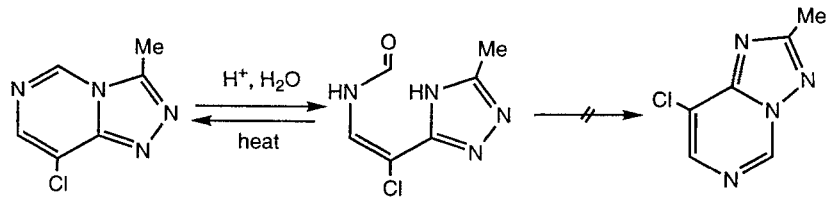
2. *Intramolecular Cyclization of 1,2,4-Triazoles Having a -C-C-N-C- Appendage at C3*

Treatment of the 8-chloro-3-methyl-1,2,4-triazolo[4,3-*c*]pyrimidine **61** with aqueous acids caused pyrimidine ring opening to give the 2-chloro-1-formamido-2-(5-methyl-1,2,4-triazolo-3-yl)ethene **62.** The latter underwent thermal dehydrative recyclization to the starting **61** [89H(28)239]. The corresponding 1,2,4-triazolo[1,5-*c*]pyrimidine regioisomer **63** has not been formed during this reaction probably due to the electron-releasing effect of the C5 methyl group in **62,** which renders the



(56) (57) (58) (59) (60)

SCHEME 26



(61) (62) (63)

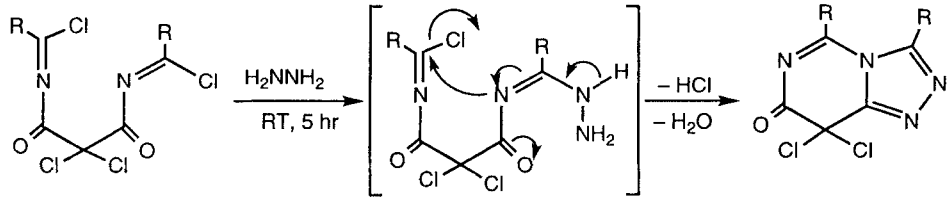
SCHEME 27

adjacent N4 of the triazole ring more nucleophilic as compared to N2 (Scheme 27).

C. Synthesis by Concurrent Formation of Both of the 1,2,4-Triazole and Pyrimidine Rings

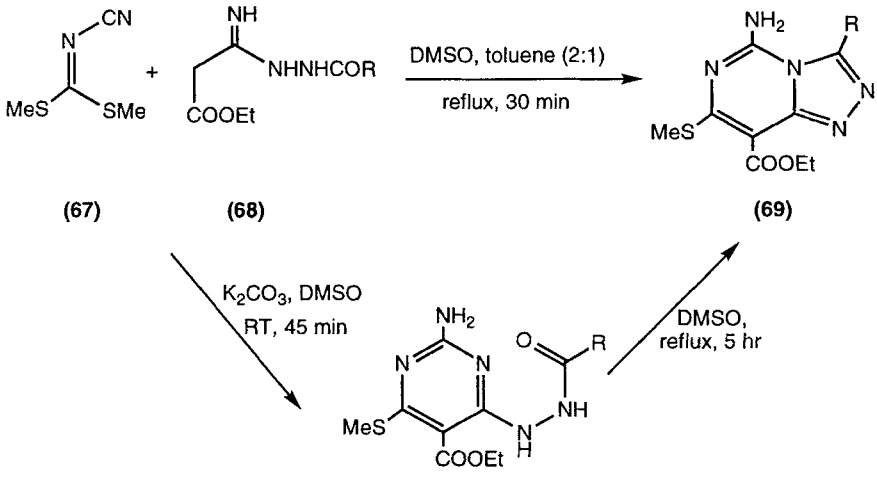
Cyclization of the 2,2-dichloromalonic acid dipyrrolidine diimidoyl dichloride **64** with hydrazine hydrate caused concurrent double ring closure to afford the 8,8-dichloro-3,5-dipyrrolidino-1,2,4-triazolo[4,3-*c*]pyrimidin-7(8*H*)-one **66** as explained in scheme 28 (86CB129).

Reaction of *N*-[bis(methylthio)methylene]cyanamide (**67**) with the N^1-acylamidrazones (**68**) at elevated temperature gave directly the corresponding 1,2,4-triazolo[4,3-*c*]pyrimidines **69.** Carrying out the reaction between **67** and **68** at ambient temperature in the presence of potassium carbonate afforded the 4-acylhydrazino-pyrimidines **70,** which were dehydratively cyclized to **69** by heating in dimethylsulfoxide (92JHC1341) (Scheme 29).



(64) (65) (66)

SCHEME 28

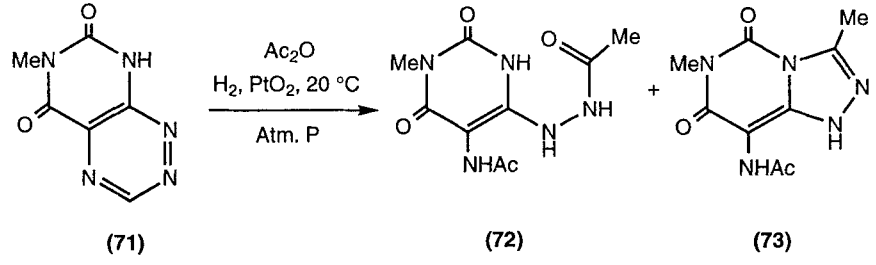


R = Me, Me_2CH, $PhCH_2$, 4-$ClC_6H_4CH_2$, Ph, 4-$O_2NC_6H_4$, 4-Pyridyl

SCHEME 29

D. SYNTHESIS BY REARRANGEMENT OF PYRIMIDO[5,4-*e*]1,2,4-TETRAZINES

Hydrogenation of the antibiotic reumycin {6-methylpyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione} **71** in acetic anhydride and in the presence of platinium (IV) oxide at ambient temperature and atmospheric pressure gave, among other products, 5-acetamido 6-acetylhydrazino-1,2,3,4-tetrahydro-3-methylpyrimidine-2,4-dione (**72**) and 8-acetamido-3,6-dimethyl-1,5,6,7-tetrahydro-1,2,4-triazolo[4,3-*c*]pyrimidine-5,7-dione (**73**) (81KPS85) (Scheme 30). Compound **72** was formed as a result of hydrogenolytic cleavage of the 1,2,4-triazine ring of **71** followed by di-*N*-acetylation. Dehydrocyclization of **72** gave **73.**



SCHEME 30

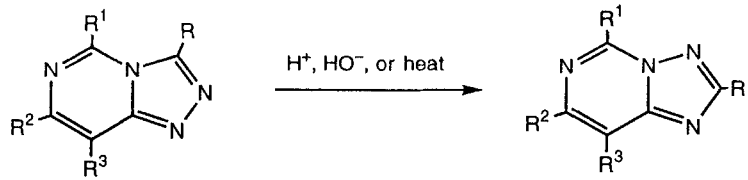
III. Reactions

A. Isomerization (Dimroth Rearrangement)

Similar to the acid-, base-, or thermal-induced Dimroth rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidines to the corresponding [1,5-*a*]regioisomers [93AHC(57)81; 99AHC(73)131], the kinetically favored 1,2,4-triazolo[4,3-*c*]pyrimidines (**16**) isomerize under the same conditions to the respective thermodynamically more stable [1,5-*c*] regioisomers **22** (Scheme 31).

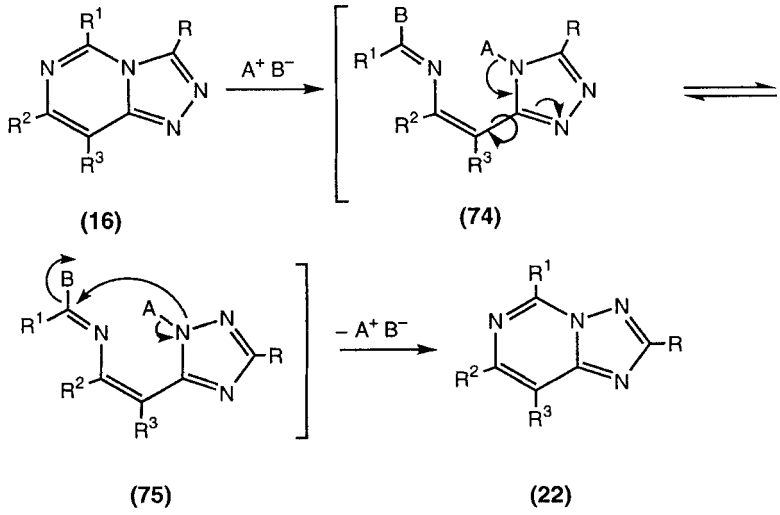
Various acid media were employed to induce this isomerization: aqueous hydrochloric acid (61BRP859287; 62BRP898409; 63JCS5642; 68JOC530), formic acid (65JCS3357; 75JHC551; 78AJC2505; 84EUP121341; 89JHC687; 90T3897; 93EUP521768), acetic acid (63JCS5642; 78AJC2505), or phosphoryl chloride (62BRP897870; 70CB3278). Utilized basic media were aqueous sodium hydroxide (62BRP898409; 65JCS3357, 65JCS3369; 75JHC551; 79KGS262), sodium methoxide in methanol (98TL3865), sodium ethoxide in ethanol (92KGS225; 93KGS1545; 94JMC2371; 95MIP1, 95MIP2), or ammonia in methanol (89JHC991). With any of these acidic or basic media, the isomerization was expedited by heat (63JCS5642; 78AJC2505). In some cases, heating or aging in water [62BRP898409; 79AJC2713; 97JCS(P2)49], methanol [81USP4269980; 97JCS(P2)49], ethanol [97JCS(P2)49], or ethyl formate (86USP4591588) sufficed to commence this rearrangement. Finally, fusion has also been applied to transform **16** to **22** (62BRP898409; 63JCS5642; 65JCS3357; 78AJC2505; 79AJC1585; 86TL3127; 96JHC1307).

The generally accepted mechanism for the acid- or base-catalyzed Dimroth rearrangement of 1,2,4-triazolo[4,3–*c*]pyrimidines (**16**) to the corresponding [1,5-*c*] isomers (**22**) is outlined in scheme 32 (63JCS5642; 68JOC530; 78AJC2505; 90T3897; 92KGS225). The rate-determining step involves the rupture of the N4–C5 bond of **16** to from the triazole intermediate **74** (78AJC2505). Recyclization of the tautomeric structure **75** at the more nucleophilic N2 of the triazole ring affords **22** (71JHC643; 78AJC2505).



(16) **(22)**

Scheme 31



SCHEME 32

UV spectrophotometric follow up of the rearrangement of the parent **16** (R-R^3=H) with acetic acid at 40°C revealed the gradual change of the three absorption maxima at 249, 258, and 269 nm of **16** to a single maximum at 265 nm of the triazole intermediates **74** and **75** (R-R^3=H) which slowly gives way to another single peak at 255 nm of the parent [1,5-*c*] regioisomer **22** (R-R^3=H) (78AJC2505).

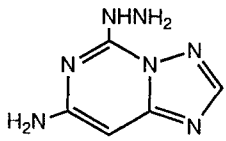
At pH 3, the hydrolytic cleavage of the N4–C5 bond of the parent **16** is about 175 times faster than cleavage of the same bond in 1,2,4-triazolo[4,3-*a*]pyrimidine; at pH 11 the rate was only 3 times faster (77AJC2515; 78AJC2505).

Dimroth rearrangement of 1,2,4-triazolo[4,3-*c*] to [1,5-*c*]pyrimidines is accompanied by marked changes in ^{1}H-NMR absorptions, permitting structural distinction in most cases (78AJC2505; 79AJC1585) (see Section IV,C).

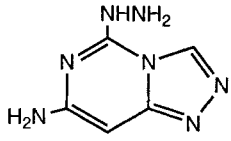
Electronic and steric factors exert their impacts on this rearrangement. Thus, the rate of isomerization increased with electron depletion and decreased with electron enrichment of the pyrimidine ring. It was less facile when the triazole ring was substituted (89JHC687). Methyl groups with a positive mesomeric effect at C5 and/or C8 (**16,** R^1 and or R^3=Me) diminished the rate of acid-induced isomerization (pH 4) by retarding the approach of the nucleophile to C5 by electronic and (for C5) steric hinderance effects. Methyl groups at C3 and/or C7 (**16,** R and or R^2=Me) exerted little electronic and no steric effects on C5, yet promoted the approach of the

electrophilic part of the reagent (A^+) to N4 as a result of enhancing the electron density on the latter (78AJC2505).

In only one case has a retro-Dimroth rearrangement of 1,2,4-triazolo[1,5-*c*] to [4,3-*c*]pyrimidine been reported, according to which the 7-amino-5-hydrazino-1,2,4-triazolo[1,5-*c*]pyrimidine **76** gave the respective [4,3-*c*] isomer **77** (79KGS262).



(76)



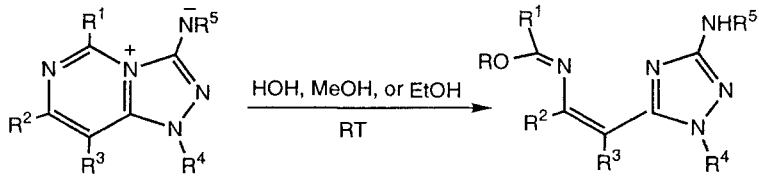
(77)

The mesoionic 1-alkyl-1,2,4-triazolo[4,3-*c*]pyrimidinium-3-aminides **37** were incapable of undergoing Dimroth rearrangement; the 5-alkenyl-1,2,4-triazolo[4,3-*c*]pyrimidines **78,** formed as a consequence of pyrimidine ring lysis with water, methanol, or ethanol at room temperature, were incapable of recyclization [97JCS(P2)49] (Scheme 33).

B. Cleavage Reactions

1. *Pyrimidine Ring Cleavage*

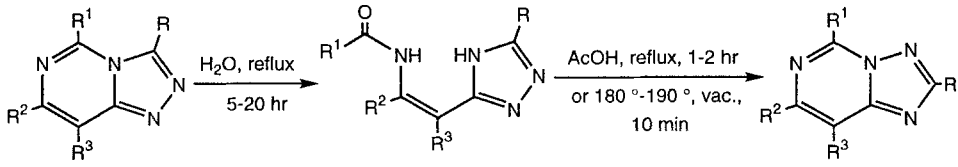
Prolonged heating of 1,2,4-triazolo[4,3-*c*]pyrimidines (**16**) with water caused pyrimidine ring cleavage and afforded the 3-[1-(acylamino)-ethen-2-yl]-1,2,4-triazoles **79.** Compounds **79** are the acyclic intermediates



(37) **(78)**

R = H, Me, Et

Scheme 33



(16) (79) (22)

R – R^3 = H or alkyl

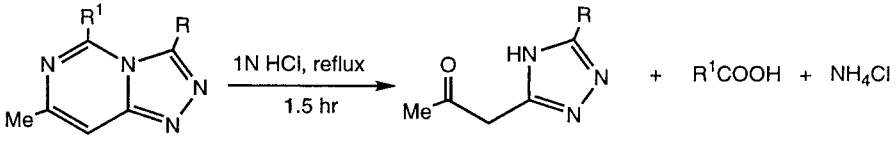
SCHEME 34

involved in Dimroth rearrangement of **16** in aqueous media; their acid-catalyzed or thermal dehydrocyclization produced the thermodynamically more stable 1,2,4-triazolo[1,5-*c*]pyrimidines **22** (78AJC2505) (Scheme 34).

Treatment of the 3-amino- or 3-mercapto-1,2,4-triazolo[4,3-*c*]pyrimidines **80** with aqueous hydrochloric acid at reflux caused further fragmentation of the pyrimidine ring to give the 3-acetonyl-5-amino- or 5-mercapto-1,2,4-triazoles **81** in addition to the corresponding alkanoic acid (63JCS5642; 65JCS3369) (Scheme 35).

2. *Triazole Ring Cleavage*

Very few reports dealt with the triazole ring cleavage of 1,2,4-triazolo-[4,3-*a*]pyrimidines [99AHC(73)131]; nevertheless, none, so far, were reported to investigate the cleavage of 1,2,4-triazolo[4,3-*c*]pyrimidines at their triazole ring.



(80) (81)

R = NH_2 , SH; R^1 = alkyl

SCHEME 35

C. Acylation and Alkylation

1. *N-Acylation*

Acylation of groups attached to 1,2,4-triazolo[4,3-*c*]pyrimidines may cause a concurrent Dimroth rearrangement. Thus, acid-catalyzed acetylation of 8-amino-7-chloro-3-oxo-1,2,4-triazolo[4,3-*c*]pyrimidine (**82**) gave the 8-acetamido-7-chloro-2-oxo-1,2,4-triazolo[1,5-*c*]pyrimidine **83** (68JOC530) (Scheme 36).

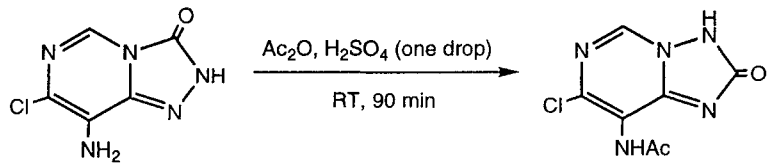
Acetylation of the 3-amino-7-methyl-5-propyl-1,2,4-triazolo[4,3-*c*]pyrimidine **84** in the presence of sodium carbonate, however, gave the 2-acetyl-3-imino derivative **86** rather than the expected 2-acetamido derivative **85;** no Dimroth rearrangement products were observed (63JCS5642) (Scheme 37).

Structure **86** was in agreement with its IR and ^{1}H-NMR spectral data and was further corroborated by an unequivocal synthesis that involved heterocyclization of the acetylhydrazinopyrimidine **87** with cyanogen chloride (63JCS5642) (Scheme 38).

No rationale has been offered as to whether such an unexpected result is due to the acetylation of the tautomeric structure **90** or due to an intramolecular acetyl migration of the initially formed 2-acetamido derivative **85** (Scheme 39).

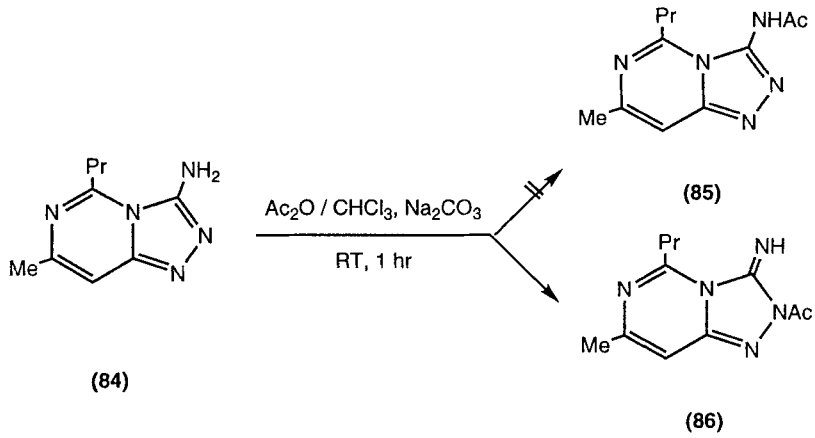
2. *N-Alkylation*

N-Alkylation of triazolopyrimidines has been made with dialkyl sulfates or alkyl halides in alkaline media. Alkylation of the 2-oxo- and 5-oxo-1,2,4-triazolo[4,3-*c*]pyrimidines **25** and **92** took place at the nitrogen atom adjacent to the carbonyl function in each case to give the N2-alkylated **91** (68JOC530; 94JMC2371) and N6-alkylated derivatives **93** (60G1821;



(82) **(83)**

Scheme 36

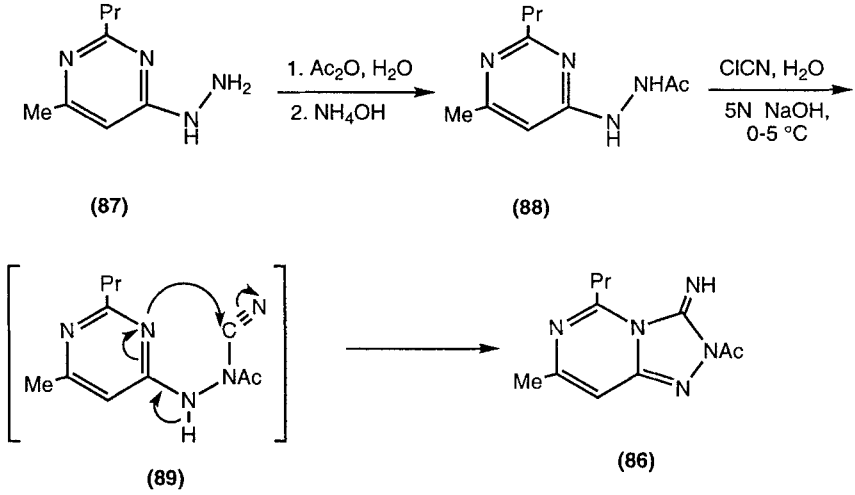


SCHEME 37

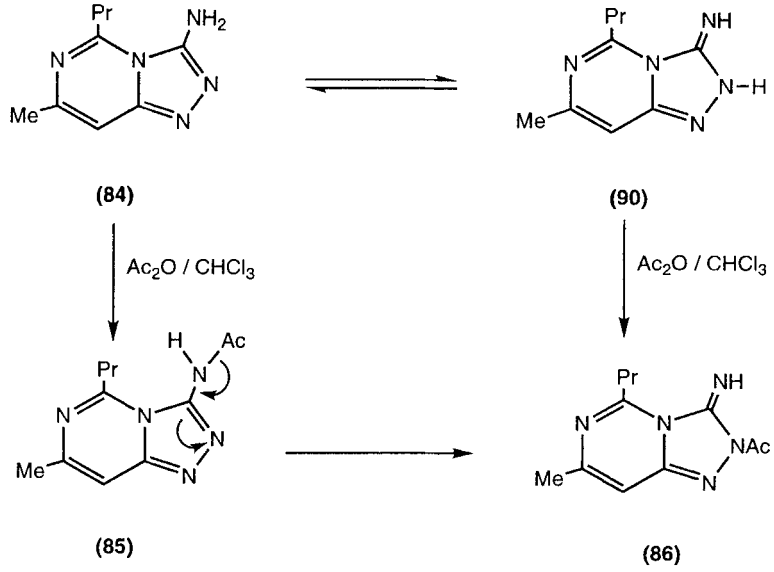
70GEP2018550) respectively (Scheme 40). In spite of the utilized strong alkaline media, no Dimroth rearrangement was reported.

3. *S-Alkylation*

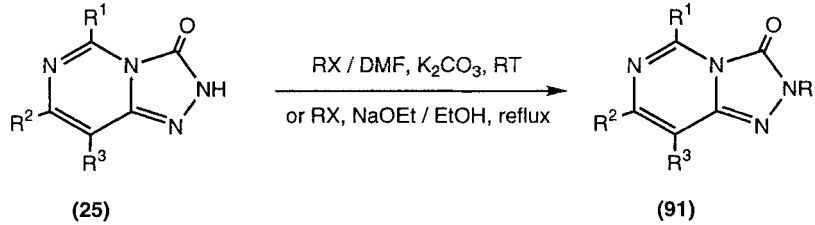
S-Alkylation of 2-mercapto-1,2,4-triazolo[4,3-*c*]pyrimidine (**94**) [94JCR (S)412; 95MIP1] or their sodium salts (79AJC2713) gave the corresponding 2-alkylmercapto derivatives **95** (Scheme 41).



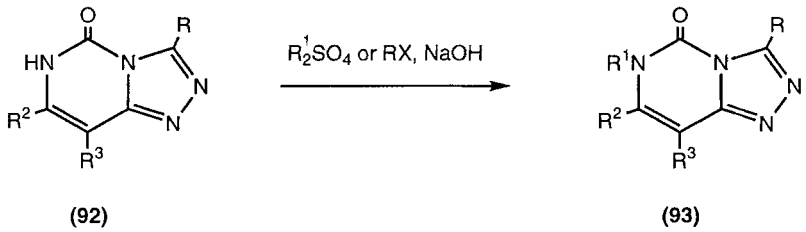
SCHEME 38



SCHEME 39

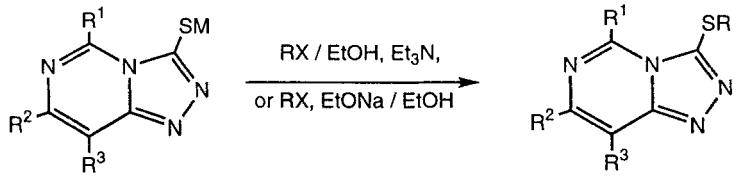


R = Me, CH_2COOEt, CH_2CH_2OH, CH_2Ph



R^1 = Me, Pr, $PhCH_2$

SCHEME 40



(94) (95)

M = H, Na; R = Me, Et, $PhCH_2$,CH_2CONH_2, CH(Me) $CONH_2$

SCHEME 41

D. NUCLEAR SUBSTITUTION

Nuclear substitution reactions of the 1,2,4-triazolo[4,3-*c*]pyrimidine system are scantily studied. A few examples concerned with bromination and nitration were reported, both of which occurred at the π-deficient pyrimidine ring.

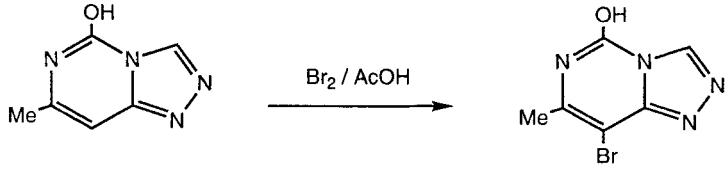
1. *Bromination*

Bromination of 5-hydroxy-7-methyl-1,2,4-triazolo[4,3-*c*]pyrimidine (**96**) led to the introduction of the bromo function into the only available site in the pyrimidine ring (C8 of **96**) to afford **97** (60G1821) (Scheme 42).

Dehydrogenative heterocyclization of the 4-arylidenehydrazino-6-methyl-2-methylthiopyrimidines **98** with bromine in acetic acid effected simultaneous bromination at C8 to produce **99.** The structure of compounds **99** was ratified by the alternative heterocyclization of the 4-arylidenehydrazino-5-bromo-6-methyl-2-methylthiopyrimidines **100** [94JCR(S)412] (Scheme 43).

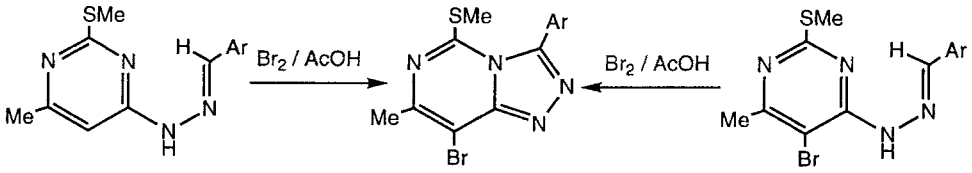
2. *Nitration*

Treatment of **96** with a mixture of concentrated nitric and sulfuric acids gave the 8-nitro derivative **101** (60G1821) (Scheme 44).



(96) (97)

SCHEME 42



(98) (99) (100)

Ar = 4-ClC_6H_4, 4-$O_2NC_6H_4$

SCHEME 43

E. SUBSTITUENT TRANSFORMATIONS

La Noce and Giuliani (75JHC551) claimed the displacement of the 5-hydroxy function of **96** by a chloro group upon heating with phosphoryl chloride in DMF to give **102**. The reverse reaction was effected by heating with 4% aqueous sodium hydroxide (Scheme 45). Surprisingly, the authors reported that no Dimroth rearrangement took place.

Hydrazinolysis of the 5-chloro function of **103** gave, mainly, the corresponding 5-hydrazino compound **105** (75JHC551; 79AJC1585) together with the 1,2-bis(triazolopyrimidin-5-yl)hydrazine **106** (75JHC551). The 5-methylthio group of **104** underwent a similar displacement to give only **105** (79AJC1585) (Scheme 46).

Thiol-to-hydroxyl group transformation has been oxidatively performed on **107** with nitric acid to give **109** (60G1821). A similar result was accomplished by hydrolytic displacement of the thiol group of **108** with an aqueous solution of sodium hydrogen carbonate (60G1830) (Scheme 47).

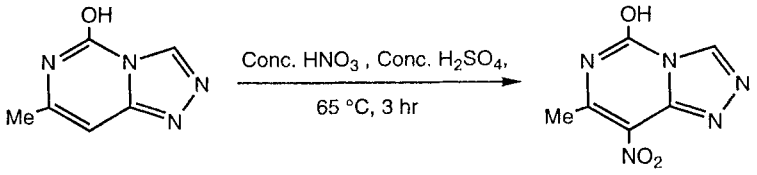
Reduction of the 8-nitro group of **111** without running the risk of nuclear reduction was achieved by catalytic hydrogenation to give the corresponding 8-amino derivative **112** [60G1821; 66JOC900; 70JCS(C)139] (Scheme 48).

Nuclear reduction also did not take place during catalytic hydrogenolysis of the 8-benzyloxy group of **113;** the corresponding 8-hydroxy compound **114** was obtained (86TL3127; 89JHC687, 89JHC991) (Scheme 49).

IV. Spectral and Electronic Properties

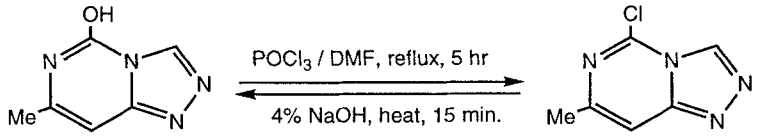
A. INFRARED SPECTRA

In the solid state, infrared absorption data indicated the preponderance of the 3-oxo **25** an the 5-oxo **92** structures (amide tautomers) over the 3-



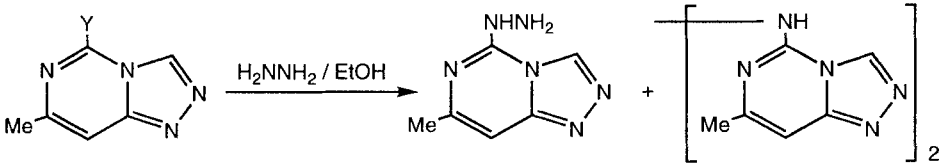
(96) **(101)**

SCHEME 44



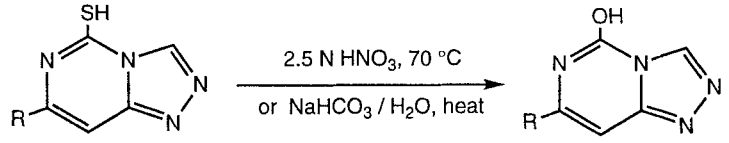
(96) **(102)**

SCHEME 45



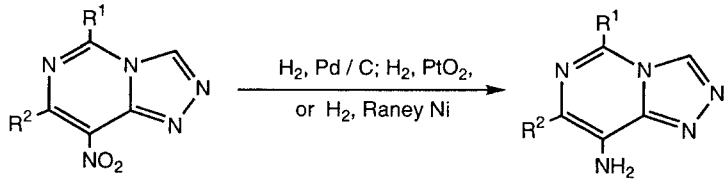
(103), Y = Cl; **(104)**, Y = SMe **(105)** **(106)**

SCHEME 46



(107), R = Me; **(108)**, R = H **(109)**, R = Me; **(110)**, R = H

SCHEME 47



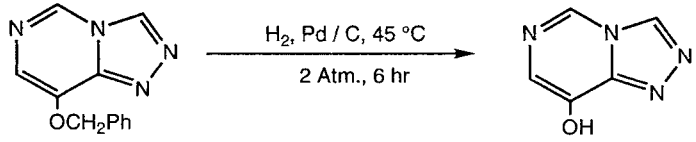
(111) **(112)**

SCHEME 48

hydroxy **115** and 5-hydroxy **116** structures (imidic acid tautomers) (63JOC2257; 65JCS3357; 68JOC530; 75JHC551) (Scheme 50).

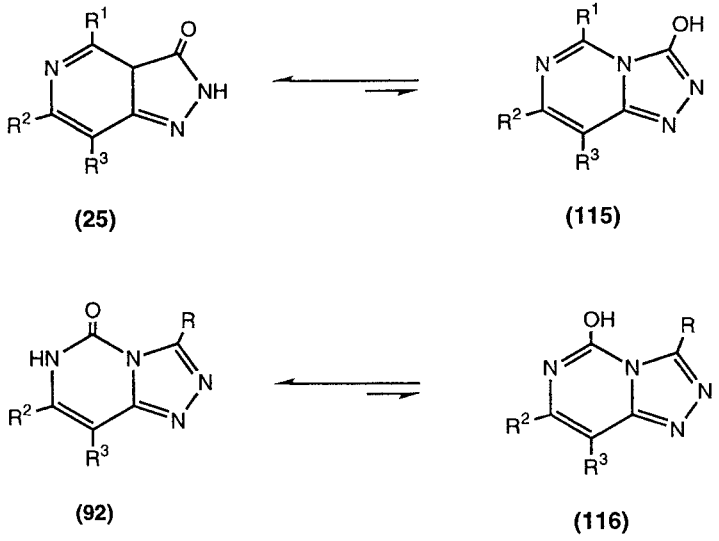
B. ULTRAVIOLET SPECTRA

Generally, 1,2,4-triazolo[4,3-*c*]pyrimidines possess characteristic UV absorptions that were attributed to π-π^* and n-π^* transitions (89JHC687). Ultraviolet data are very helpful in differentiating between the [4,3-*c*] and [1,5-*c*] regioisomers [60G1821, 60G1830; 63JCS5642, 63JOC2257; 65JCS3357, 65JCS3369; 68JOC530; 70JCS(C)139; 75CPB1885; 78AJC2505; 89JHC687; 95JOC7066]. Various alkyl-substituted 1,2,4-triazolo[4,3-*c*]pyrimidines showed two absorption bands at 250–260 and 260–270 nm, which may be flanked by two inflexions or shoulders; the corresponding [1,5-*c*] regioisomers revealed only a single band at 250–260 nm, which may be accompanied by a minor inflexion (78AJC2505). 3-Amino-1,2,4-triazolo[4,3-*c*]pyrimidines absorbed at three regions: 202–209, 260–267, and 310–321 nm; the corresponding 2-amino-1,2,4-triazolo[1,5-*c*] pyrimidines absorbed at 226–230, 259–270, and 283–303 nm (63JCS5642).



(113) **(114)**

SCHEME 49



(25) (115)

(92) (116)

SCHEME 50

C. ^{1}H-NMR SPECTRA

Sufficient data are available at present to justify drafting some general guidelines correlating the structure of 1,2,4-triazolo[4,3-*c*]pyrimidines and their ^{1}H-NMR spectra [68JOC530; 70CB3278, 70JCS(C)139; 72JCS-(P1)2316; 75CPB1885, 75JHC551; 78AJC2505, 78TL2071; 79AJC1585, 79AJC2713; 86TL3127; 89JHC687]. To this field of investigation, the contributions of D. J. Brown and his group are very valuable (78AJC2505; 79AJC1585, 79AJC2713); in addition to the parent 1,2,4-triazolo[4,3-*c*]- and [1,5-*c*]pyrimidines, this Australian group prepared and recorded the ^{1}H-NMR spectra of a large number of the mono-, di-, tri-, and tetramethyl derivatives (**117–120**).

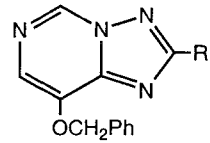
(117) a = H; b, c, d, or e = H or Me **(118)**

(119) a = Me; b, c, d, or e = H or Me **(120)**

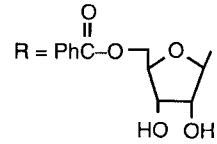
Some of the useful guidlines to correlate the structure and ^{1}H-NMR data of these compounds are (1) the decreasing order of magnitude (ppm) of the chemical shifts (direction to higher magnetic field) of the CH protons of the [4,3-*c*] compounds **117** and **119** is almost always C5–H > C3–H > C7–H > C8–H; (2) the same order holds true for the chemical shifts of methyl groups of the various methyl derivatives of **117** and **119,** i.e., C5–Me > C3–Me > C7–Me > C8–Me; and (3) a definitive distinction can be made between a particular [4,3-*c*] compound **117** and its [1,5-*c*] isomer **118;** the C3–H signal of the former invariably appears at 0.45–1.25 ppm higher than the C2–H signal of the latter. Similarly, the C3–Me signal of a particular [4,3-*c*] compound **119** always appeared at 0.25–0.40 ppm higher than the C2–Me signal of the corresponding [1,5-*c*] isomer **120.**

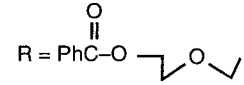
The hydrogen and carbon atoms of the 3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*c*]pyrimidine *C*-nucleoside **121** and acyclo *C*-nucleoside **122** as well as their regioisomeric 2-β-D-ribofuranosyl-1,2,4-triazolo[1,5-*c*]pyrimidine *C*-nucleoside **123** and acyclo *C*-nucleoside **124** were unequivocally assigned by recording their two-dimensional ^{1}H–^{13}C-correlated NMR spectra (89MRC1001).

(121), (122)



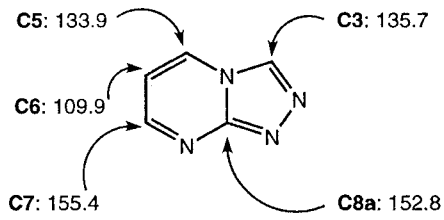
(123), (124)

(121), (123) 

; **(122), (124)** 

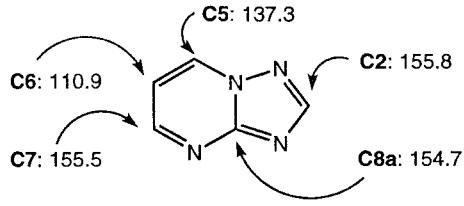
D. ^{13}C-NMR Spectra

Differences in ^{1}H-NMR chemical shifts of 1,2,4-triazoloazines are sometimes too small to permit sharp structural distinction between closely related isomer pairs, particularly those emanating from isomerization of kinetically preferable to thermodynamically more stable compounds. In such cases, ^{13}C-NMR spectroscopy proved very beneficial (79OMR385; 87JHC805). Thus, Pugmire *et al.* (87JHC805) studied the ^{13}C-NMR spectral



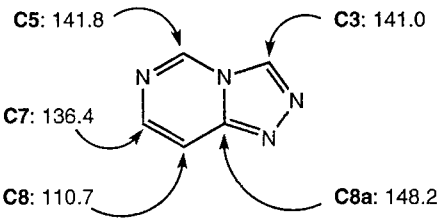
δ : C7 > C8a > C3 > C5 > C6

(125)



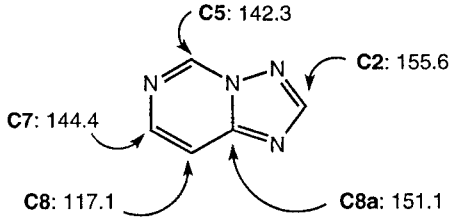
δ : C2 > C7 > C8a > C5 > C6

(126)



δ : C8a > C5 > C3 > C7 > C8

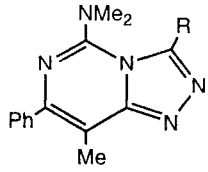
(127)



δ : C2 > C8a > C7 > C5 > C8

(128)

data of the four 1,2,4-triazolo[4,3-*a*]-, [1,5-*a*]-, [4,3-*c*]-, and [1,5-*c*]pyrimidine systems **125–128** and found that they exhibit large systematic and clearly definitive ^{13}C-NMR shifts. Viehe *et al.* (90T3897) measured the ^{13}C-NMR spectra of a number of 3-substituted-5-dimethylamino-8-methyl-7-phenyl-1,2,4-triazolo[4,3-*c*]pyrimidines (**129**).

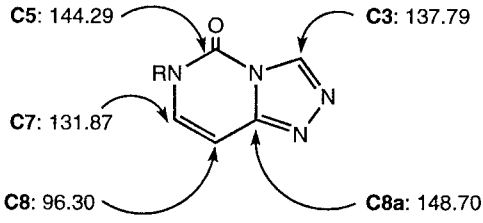


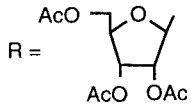
R = H, NMe_2, NHPh, $NHCH_2Ph$, $-N(CH_2)_{4-6}$

(129)

The C8a signal of **129** invariably appeared at the lowest magnetic field (highest chemical shift) and that of C8 appeared at the highest field (lowest chemical shift) of the five carbons of the ring system. The order of the chemical shifts of the three other carbons of the ring system (C3, C5, and

C7) varied with the C3 substituent. The order of the ^{13}C chemical shifts of the 6-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazolo[4,3-*c*]pyrimidin-5-one *C*-nucleoside **130** (95JOC7066) conforms with the same order for the parent heterocycle **127.**



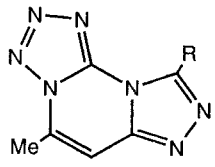


δ :C8a > C5 > C3 > C7 > C8

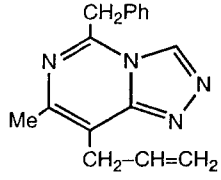
(130)

E. Mass Spectra

The electron impact mass spectra of a number of the tricyclic 5-substituted-9-methyl-1,2,4-triazolo[4,3-*c*]tetrazolo[1,5-*a*]pyrimidines **131** were reported (79OMS227). Tricyclic intermediates were proposed to explain the mass spectral fragmentation of the 8-allyl-5-benzyl-7-methyl-1,2,4-triazolo[4,3-*c*]pyrimidine **132** (93KGS1545).



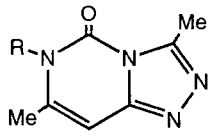
(131)

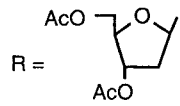


(132)

F. X-Ray

X-ray crystallographic analysis would be the method of choice for assigning the structure of closely related and easily isomerizable compounds such as 1,2,4-triazolo[4,3-*c*]pyrimidines. Thus, X-ray analysis of the 6-(3,5 di-*O*-acetyl-2-deoxy-β-D-ribofuranosyl)-3,7-dimethyl-1,2,4-triazolo[4,3-*c*] pyrimidin-5-one **133** confirmed the assigned structure (98TL3865).

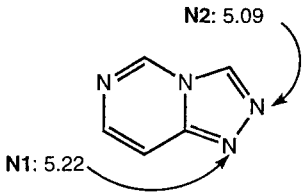




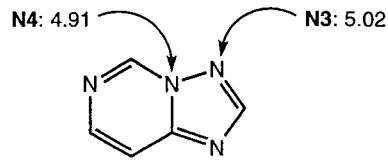
(133)

G. Electronic Properties

The electron densities of the parent 1,2,4-triazolo[4,3-*c*]- and [1,5-*c*]-pyrimidines (**127** and **128**) were calculated; the total π-electron density was obtained from HMO calculations and the total electron density by the complete neglect of differential overlap approximation method (CNDO-2). Whereas N6 caused C5 of both systems to be more electrophilic, N2 in the [4,3-*c*] system **127** decreased the π-electron density at C5 more than N3 in the [1,5-*c*] system **128** at the same carbon. The calculations also indicated that the driving force for the **127**-to-**128** rearrangement should originate from the larger interaction between N1 and N2 in the [4,3-*c*] system **127** (electron densities, 5.22 and 5.09, respectively) compared to the interaction between N3 and N4 in the [1,5-*c*] system **128** (electron densities, 5.20 and

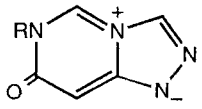


(127)

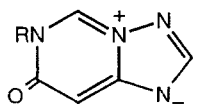


(128)

4.91, respectively) (71JHC643). The electronic structures of mesoionic 1,2,4-triazolo[4,3-*c*]- and [1,5-*c*]pyrimidin-7-ones (**134** and **135**) have been investigated via variable-electronegativity Praiser–Parr–Popple–SCF π-molecular orbital calculations (73JHC479).

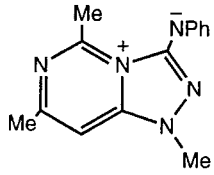


(134)

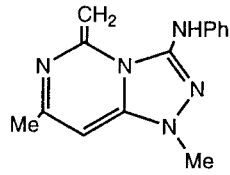


(135)

The structure and electronic properties of 1,5,7-trimethyl-1,2,4-triazolo-[4,3-*c*]pyrimidinium-3-phenylaminide (**136**) was studied using semiempirical and *ab initio* calculations. The mesoionic structure **136** is unexpectedly more stable than its theoretically possible tautomer **137** [97JCS(P2)49]. Optimization of the molecular structure of **136** pinpointed a planar conformation from which the phenyl group is twisted by an angle of approximately 30° [97JCS(P2)49].



(136)



(137)

V. Applications

In contrast to compounds belonging to the 1,2,4-triazolo[1,5-*a*]- and [4,3-*a*]pyrimidines, which are widely used in photography [93AHC(57)81; 99AHC(73)131], and some of the [1,5-*a*] compounds, which are used as agrochemicals [93AHC(57)81], none of these applications were reported for compounds of the [4,3-*c*] system. Nevertheless, many compounds of the latter system exhibit multifaceted medicinal and biological activities. Thus, for the treatment of respiratory system disorders, they show bronchodilator (62BRP898408; 84EUP121341; 85USP4532242), antiasthmatic, and bronchiolytic activities (70GEP2018550). For the urinary tract, they reveal diuretic (81GEP3029871; 83USP4405780) and anti-infection activities (71GEP2004713). Applications to the cardiovascular system include uses for treating hypotensive (60G1821, 60GEP1074589; 94JMC2371, 94USP53358950) and antiarrythmic disorders (92PJC131) and of cardiac insufficiency and disease of the arterial wall (94USP5358950). In addition, they show tranquilizing (81USP4269980), antirheumatoidal (62BRP 898408), and antibacterial activities (71GEP2004713; 79AJC2713).

References

56JPJ804 D. Shiho, S. Tagami, N. Takahayashi, and R. Honda, *J. Pharm. Soc. Jpn.* **76,** 804 (1956) [*CA* **51,** 1196 (1957)].

57JCS727 J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 727 (1957).

60G1821 B. Camerino, G. Palamidessi, and R. Sciaky, *Gazz. Chim. Ital.* **90,** 1821 (1960) [*CA* **57,** 7261 (1962)].

60G1830 B. Camerino, G. Palamidessi, and R. Sciaky, *Gazz. Chim. Ital.* **90,** 1830 (1960) [*CA* **57,** 7262 (1962)].

60GEP1074589 Farmaceutici Italia Soc. anon. (B. Camerino and T. La Noce), Ger. Pat. 1,074,589 (1960) [*CA* **55,** 19967 (1961)].

61BRP859287 Imperial Chemical Industries, Ltd. (G. W. Miller and F. L. Rose), Br. Pat. 859,287 (1961) [*CA* **55,** 17666 (1961)].

62BRP897870 Imperial Chemical Industries Ltd. (G. W. Miller and F. L. Rose), Br. Pat. 897,870 (1962) [*CA* **58,** 10212 (1963)].

62BRP898408 Imperial Chemical Industries Ltd. (G. W. Miller and F. L. Rose), Br. Pat. 898,408 (1962) [*CA* **57,** 11210 (1962)].

62BRP898409 Imperial Chemical Industries Ltd. (G. W. Miller and F. L. Rose), Br. Pat. 898,409 (1962) [*CA* **57,** 11209 (1962)].

63JCS5642 G. W. Miller and F. L. Rose, *J. Chem. Soc.,* 5642 (1963).

63JOC2257 C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.* **28,** 2257 (1963).

64BRP951652 Imperial Chemical Industries Ltd. (W. Broadbent, G. W. Miller, and F. L. Rose) Br. Pat. 951652 (1960) [*CA* **61,** 3121 (1964)].

65JCS3357 G. W. Miller and F. L. Rose, *J. Chem. Soc.,* 3357 (1965).

65JCS3369 W. Broadbent, G. W. Miller, and F. L. Rose, *J. Chem. Soc.,* 3369 (1965).

66JOC900 T. K. Liao, F. Baiocchi, and C. C. Cheng, *J. Org. Chem.* **31,** 900 (1996).

66MI1 L. Giammanco, *Atti Accad. Sci., Lett. Arti Palermo, Parte I* **27,** 449 (1966/1967) [*CA* **72,** 21673 (1970)].

68JOC530 C. Temple, Jr., B. H. Smith, Jr., and J. A. Montgomery, *J. Org. Chem.* **33,** 530 (1968).

70CB3278 H. Reimlinger, *Chem. Ber.* **103,** 3278 (1970).

70GEP2018550 Imperial Chemical Industries Ltd. (G. J. Stacey), Ger. Pat. Offen. 2,018,550 (1970) [*CA* **74,** 22873 (1971)].

70JCS(C)139 M. E. C. Biffin, D. J. Brown, and T. Sugimoto, *J. Chem. Soc. C,* 139 (1970).

71AJC633 D. J. Brown and T. Sugimoto, *Aust. J. Chem.* **24,** 633 (1971).

71GEP2004713 H. Berger, R. Gall, H. Merdes, K. Stach, W. Sauer, and W. Voemel, Ger. Pat. Offen. 2,004,713 (1971) [*CA* **75,** 118338 (1971)].

71JHC643 P. Guerret, R. Jacuier, and G. Maury, *J. Heterocycl. Chem.* **8,** 643 (1971).

71MI1 A. Spasov and N. Spasova, *Dokl. Bolg. Akad. Nauk* **24,** 247 (1971) [*CA* **75,** 5841 (1971)].

72JCS(P1)2316 D. J. Brown and J. R. Kershaw, *J. Chem. Soc., Perkin Trans. I,* 2316 (1972).

73JHC479 R. A. Coburn, R. A. Carapellotti, and R. A. Glennon, *J. Heterocycl. Chem.* **10,** 479 (1973).

75CPB1885 F. Yoneda and T. Nagamatsu, *Chem. Pharm. Bull.* **23,** 1885 (1975).

75JHC551 T. La Noce and A. M. Giuliani, *J. Heterocycl. Chem.* **12,** 551 (1975).

76MI1 V. V. Korshak, L. A. Rusanov, M. K. Kereselidze, and T. K. Dzhashiashvili, *Izv. Akad. Nauk Gruz. SSR, Ser. Khim.* **2,** 39 (1976) [*CA* **85,** 123862 (1976)].

76S833 B. Jenko, B. Stanovnik, and M. Tisler, *Synthesis,* 833 (1976).

77AJC2515 D. J. Brown and T. Nagamatsu, *Aust. J. Chem.* **30,** 2515 (1977).

77TL2187 A. Koennecke and E. Lippmann, *Tetrahedron Lett.,* 2187 (1977).

78AJC2505 D. J. Brown and T. Nagamatsu, *Aust. J. Chem.* **31,** 2505 (1978).

78MI1 H. Hayatsu, A. Kitajo, K. Sugihara, N. Nitta, and K. Negishi, *Nucleic Acids Res., Spec. Publ.* **5,** 315 (1978) [*CA* **90,** 121937 (1979)].

78PJC37 W. E. Hahn and E. Kozlowska-Gramsz, *Pol. J. Chem.* **52,** 37 (1978) [*CA* **89,** 43301 (1978)].

78TL2071 A. Koennecke, R. Doerre, and E. Lippmann, *Tetrahedron Lett.,* 2071 (1978).

79AJC1585 D. J. Brown and T. Nagamatsu, *Aust. J. Chem.* **32,** 1585 (1979).

79AJC2713 D. J. Brown, G. W. Grigg, Y. Iwai, K. N. McAndrew, T. Nagamatsu, and R. Van Heeswyck, *Aust. J. Chem.* **32,** 2713 (1979).

79KGS262 N. V. Volkova, V. N. Konyukhov, T. G. Koksharova, L. N. Dianova, and Z. V. Pushkareva, *Khim. Geterotsikl. Soedin.,* 262 (1979) [*CA* **90,** 204017 (1979)].

79OMR385 A. Koennecke, E. Kleinpeter, and E. Lippmann, *Org. Magn. Reson.* **12,** 385 (1979) [*CA* **92,** 57961 (1980)].

79OMS227 A. Koennecke, P. Lepom, R. Doerre, and E. Lippmann, *Org. Mass Spectrom.* **14,** 227 (1979) [*CA* **91,** 192284 (1979).

80AJC1147 D. J. Brown and K. Shinozuka, *Aust. J. Chem.* **33,** 1147 (1980).

81GEP3029871 G. D. Searle and Co. (H. A. Wagner), Ger. Pat. Offen. 3,029,871 (1981) [*CA* **94,** 175163 (1981)].

81KPS85 S. E. Esipov, N. A. Klyuev, L. A. Saburova, and V. M. Adanin, *Khim. Prir. Soedin.,* 85 (1981) [*CA* **95,** 24999 (1981)].

81USP4269980 American Cyanamid Co. (R. A. Hardy, Jr., J. S. Baker, and N. Q. Quinones), U. S. Pat. 4,269,980 (1981) [*CA* **95,** 62258 (1981)].

83USP4405780 G. D. Searle and Co. (H. Wagner), U. S. Pat. 4,405,780 (1983) [*CA* **100,** 6550 (1984)].

84EUP121341 Riker Laboratories, Inc. (J. J. Wade), Eur. Pat. 121,341(1984) [*CA* **102,** 95663 (1985)].

85GEP3427823 American Cyanamid Co. (R. Paul, R. A. Hardy, Jr., and J. A. Bockman), Ger. Pat. Offen 3427823 (1985) [*CA* **104,** 5887 (1986)].

85USP4528288 Riker Laboratories, Inc. (J. J. Wade), U. S. Pat. 4,528,288 (1985) [*CA* **104,** 5889 (1986)].

85USP4532242 Riker Laboratories, Inc. (J. J. Wade), U. S. Pat. 4,532,242 (1985) [*CA* **104,** 5891 (1986)].

86CB129 W. Ried and J. Nenninger, *Chem. Ber.* **119,** 129 (1986).

86TL3127 O. Rousseaux, D. Blondeau, and H. Sliwa, *Tetrahedron Lett.* **27,** 3127 (1986).

86USP4591588 Riker Laboratories, Inc. (J. J. Wade), U. S. Pat. 4,591,588 (1986) [*CA* **105,** 97494 (1986)].

87JHC805 R. J. Pugmire, J. C. Smith, D. M. Grant, B. Stanovnik, M. Tisler, and B. Vercek, *J. Heterocycl. Chem.* **24,** 805 (1987).

89EUP343752 Dow Chemical Co. (J. C. Van Heertum, B. C. Gerwick, III, and W. A. Kleschick, Eur. Pat. 343,752 (1989) [*CA* **112,** 198409 (1990)].

89H(28)239 H. S. El-Khadem, J. Kawai, and D. L. Swartz, *Heterocycles* **28,** 239 (1989) [*CA* **111,** 77922 (1989)].

89JHC313 A. M. El-Reedy, A. S. Ali, and A. O. Ayyad, *J. Heterocycl. Chem.* **26,** 313 (1989).

89JHC687 H. Sliwa, D. Blondeau, and O. Rousseaux, *J. Heterocycl. Chem.* **26,** 687 (1989).

89JHC991 F. Dennin, O. Rousseaux, D. Blondeau, and H. Sliwa, *J. Heterocycl. Chem.* **26,** 991 (1989).

89MI1 S. Barbato, G. Piccialli, C. Santacroce, L. De Napoli, and L. Mayol, *Nucleosides Nucleotides* **8,** 515 (1989) [*CA* **112,** 21237 (1990)].

89MRC1001 F. Dennin, O. Rousseaux, D. Blondeau, and H. Sliwa, *Magn. Reson. Chem.* **27,** 1001 (1989) [*CA* **112,** 198946 (1990)].

89PHA604 A. Dlugosz, Z. Machon, and R. Jasztold-Howorko, *Pharmazie* **44,** 604 (1989).

90H(31)277 O. Rousseaux, D. Blondeau, and H. Sliwa, *Heterocycles* **31,** 277 (1990).

90JMC1230 J. B. Medwid, R. Paul, J. S. Baker, J. A. Brockman, M. T. Du, W. A. Hallett, J. W. Hanifin, R. A. Hardy, Jr., M. E. Tarrant, L. W. Torley, and S. Wrenn, *J. Med. Chem.* **33,** 1230 (1990).

90T3897 N. Guillot, H. G. Viehe, B. Tinant, and J. P. Declercq, *Tetrahedron* **46,** 3897 (1990).

91AKZ448 G. G. Danagulyan, L. G. Saakyan, P. B. Terent'ev, and M. G. Zalinyan, *Arm. Khim. Zh.* **44,** 488 (1991) [*CA* **117,** 191807 (1992)].

91MI1 S. Barbato, G. Piccialli, C. santacroce, L. De Napoli, and L. Mayol, *Nucleosides Nucleotides* **10,** 853 (1991) [*CA* **115,** 208440 (1991)].

92JHC1341 M. T. Cocco, C. Congiu, A. Maccioni, and V. Onnis, *J. Heterocycl. Chem.* **29,** 1341 (1992).

92KGS225 G. G. Danagulyan, L. G. Saakyan, and M. G. Zalinyan, *Khim. Geterotsikl. Soedin.*, 225 (1992) [*CA* **117,** 233226 (1992)].

92PJC131 A. Dlugosz, *Pol. J. Chem.* **66,** 131 (1992) [*CA* **117,** 251310 (1992)].

93EUP521768 Laboratories UPSA (N. Bru-Magniez, E. Nicolai, and J. M. Teulon), Eur. Pat. 521,768 (1993) [*CA* **119,** 49405 (1993)].

93AHC(57)81 G. Fischer, *Adv. Heterocycl. Chem.* **57,** 81(1993).

93KGS1545 G. G. Danagulyan, L. G. Saakyan, G. A. Panosyan, G. A. Bulakhov, P. B. Terentyev, and M. G. Zalinyan, *Khim. Geterotsikl. Soedin.*, 1545 (1993) [*CA* **122,** 9979 (1995)].

94JCR(S)412 A.-S. M. Abdel-Fattah, S. M. Sherif, M. M. Youssef, and N. S. E.Ahmed, *J. Chem. Res., Synop.*, 412 (1994).

94JMC2371 E. Nicolai, G. Cure, J. Goyard, M. Kirchner, J. M. Teulon, A.Versigny, M. Cazes, F. Caussade, A. Virone-Oddos, and A. Cloarec, *J. Med. Chem.* **37,** 2371 (1994).

94USP5358950 Laboratories UPSA (N. Bru-Magniez, E. Nicolai, and J.-M. Teulon), U. S. Pat. 5,358,950 (1994) [*CA* **122,** 314561 (1995)].

95JOC7066 R. W. Miles, V. Samano, and M. J. Robins, *J. Org. Chem.* **60,** 7066 (1995).

95MIP1 Dow Elanco (J. A. Orvik and D. L. Shiang), PCT Int. Appl. Wo 95/12,595 (1995) [*CA* **123,** 314003 (1995)].

95MIP2 Dow Elanco (T. A. Olmstead, M. A. Gonzales, J. A. Orvik, D. L. Pearson, J. W. Ringer, D. L. Shiang, J. J. Tai, and A. P. Wallin), PCT Int. Appl. WO 95/12,596 (1995) [*CA* **123,** 16951 (1995)].

95MIP3 Dow Elanco (J. A. Orvik and D. L. Shiang), PCT Int. Appl. WO 95/12,597 (1995) [*CA* **123,** 256756 (1995)].

96JHC1307 T. Boyer, L. Fournel, E. Nicolai, and J. M. Teulon, *J. Heterocycl. Chem.* **33,** 1307 (1996).

97JCS(P2)49 D. L. Crabb, D. A. Main, J. O. Morley, P. N. Preston, and S. H. B. Wright, *J. Chem. Soc., Perkin Trans.* **2,** 49 (1997).

98TL3865 D. Loaks, D. M. Brown, and S. A. Salisbury, *Tetrahedron Lett.* **39,** 3865 (1998).

99AHC(73)131 M. A. E. Shaban and A. E. A. Morgaan, *Adv. Heterocycl. Chem.* **73,** 13 (1999).